In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 15-520V

Filed: February 17, 2022

A.S., *a minor, by her parents,* JEREMY and KIMBERLY SVAGDIS, Petitioners, v. SECRETARY OF HEALTH AND HUMAN SERVICES, Respondent.	TO BE PUBLISHED Decision on Entitlement; DTaP Vaccine; IPV; Hib vaccine; Hep. B vaccine; Prevnar vaccine; RotaTeq vaccine; Mitochondrial Dysfunction; Encephalopathy; Infantile Spasms; Seizures.

Michael McLaren, Black McLaren, et al., PC, Memphis, TN, for Petitioners
Ronalda Kosh, U.S. Department of Justice, Washington, DC, for Respondent

DECISION ON ENTITLEMENT[1]

Oler, Special Master:

On May 21, 2015, A.S. and her parents, Jeremy Svagdis ("Mr. Svagdis") and Kimberly Svagdis ("Mrs. Svagdis") (collectively "Petitioners") filed a petition for compensation under the National Vaccine Injury Compensation Program, 42 U.S.C. § 300aa-10, *et seq.*[2] (the "Vaccine Act" or "Program") alleging, in part, that A.S. suffered from a significant aggravation of her previous neurologic and/or physical impairments that were present, to a lesser extent, prior to the allegedly causal vaccinations. Pet. at 1. For the reasons discussed in this decision, I find that

[1] This Decision will be posted on the United States Court of Federal Claims' website, in accordance with the E-Government Act of 2002, 44 U.S.C. § 3501 (2012). **This means the Decision will be available to anyone with access to the internet**. As provided in 42 U.S.C. § 300aa-12(d)(4)(B), however, the parties may object to the Decision's inclusion of certain kinds of confidential information. To do so, each party may, within 14 days, request redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). Otherwise, this Decision will be available to the public in its present form. *Id.*

[2] National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755. Hereinafter, for ease of citation, all "§" references to the Vaccine Act will be to the pertinent subparagraph of 42 U.S.C. § 300aa (2012).

Petitioners have not demonstrated that that the vaccines A.S. received significantly aggravated her condition.

I. Procedural History

Petitioners filed a petition on May 21, 2015, alleging that their minor daughter, A.S., developed infantile spasms, seizures, developmental regression/delays, epileptic encephalopathy, and/or other neurologic and/or physical impairments and other injuries that were "caused-in-fact" by the DTaP, IPV, Hib, Hep. B, Prevnar and/or RotaTeq vaccinations A.S. received on June 18, 2012; or in the alternative, that these vaccines significantly aggravated her underlying neurological condition.[3] Pet. at 1. ECF No. 1. A CD containing Exhibits 1-14 was received by the Clerk's Office on May 27, 2015. On June 15, 2015, Petitioners filed a statement of completion. ECF No. 6.

On December 10, 2015, Petitioners filed an amended petition, additional medical records, and an amended statement of completion. ECF Nos. 11-13. The amended petition added that the DTaP vaccine "resulted in the table injury of encephalopathy (or enc[]ephalitis) within 72 hours of vaccination."[4] Am. Pet. at 1. Petitioners' petition and amended petition both stated that "while there was originally some concern about [A.S.] possibly suffering from a mitochondrial disorder, that has since been ruled out by her current treating physicians."[5] Pet. at 4; Am. Pet. at 5.

On November 3, 2016, Petitioners filed expert reports written by Drs. Marcel Kinsbourne and Richard Boles. Exs. 17, 30. On March 17, 2017, Respondent filed a Rule 4(c) Report and three expert reports written by Drs. Max Wiznitzer, Christine McCusker, and Shawn McCandless. Exs. A, C, E. On August 16, 2017, Petitioners filed an expert report from Dr. Eric Gershwin. Ex. 37.

On July 27, 2018, I held a status conference with the parties to discuss a date for an entitlement hearing and concerns regarding Dr. Kinsbourne's health and ability to testify at the hearing. ECF No. 47. An entitlement hearing was set for September 5-6, 2019. *See* non-PDF Scheduling Order on 8/6/2018. On September 24, 2018, Petitioners filed a status report confirming they will rely on Dr. Kinsbourne's expert report and testimony. ECF No. 48.

On June 17, 2019, Respondent filed three supplemental reports from Drs. Wiznitzer, McCusker, and McCandless. Exs. G, H, I.

I held an entitlement hearing on September 5-6, 2019. On October 28, 2019, Petitioners filed a post-hearing statement from Dr. Kinsbourne and two additional pieces of medical literature.

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[3] Although Petitioners initially alleged A.S.'s injuries were caused in fact by her vaccines, they exclusively pursued a significant aggravation claim at hearing. *See*, e.g., Pet'rs' Pre-Hearing Brief at 7-8. ECF No. 55; Pet'rs' Post-Hearing Brief at 1, 13. ECF No. 96.

[4] Petitioners did not pursue this Table claim. *See* Joint Prehearing Submission at 2: "The parties agree that A.S. did not suffer an acute Table encephalopathy following her June 18, 2012 vaccinations as defined by the Vaccine Act." ECF No. 66.

[5] At the entitlement hearing, Petitioner's theory of the case rested on the assumption that A.S. had mitochondrial dysfunction that made her susceptible to injury from vaccination.

Ex. 59. On December 30, 2019, Respondent filed reports from Dr. Wiznitzer and McCandless. Exs. N, P. On February 13, 2020, Petitioners filed a report from Dr. Kinsbourne. Ex. 62. On May 15, 2020, Respondent filed reports from Dr. Wiznitzer and McCandless. Exs. R, S.

On July 20, 2020, Petitioners filed a status report stating they did not intend to file additional expert reports and believed the record was complete. ECF No. 93. On August 19, 2020, Respondent filed a status report stating the record was complete. ECF No. 94.

I held a status conference on September 7, 2021 where counsel and I discussed the fact that no post-hearing briefs had been filed. I indicated that briefing would be helpful to me, and set a briefing schedule. ECF No. 95.

On November 7, 2021, Petitioner filed a post-hearing brief. ECF No. 96. On December 7, 2021, Respondent filed a post-hearing brief. ECF No. 97. On January 13, 2022, Petitioners filed a status report indicating that they did not plan to file a reply brief, and that this matter was now ripe for a decision. ECF No. 99.

II. Medical Records

A. Relevant Pre-Vaccination History

A.S. was born on December 15, 2011 with no serious complications. She was released from Northside Hospital Forsyth the next day. Ex. 15 at 11, 21.

On December 19, 2011, A.S. had a routine check-up at Preston Ridge Pediatric Associates. Ex. 8 at 11. A.S. had a normal neurological exam but was noted to be jaundiced and had latching problems. *Id.* On January 9, 2012, A.S. returned to Preston Ridge Pediatric Associates for another routine check-up. *Id.* at 8. Under current problems, A.S. was noted to have "lots of drool", and gurgles and spitting, but was otherwise normal. *Id.* at 8-9. A.S.'s weight was recorded as 10-25 percentile. *Id.* at 8. A.S. was scheduled for an appointment on February 13, 2012 but did not show.

On March 8, 2012, A.S. visited Preston Ridge Pediatric Associates. Ex. 8 at 6. A.S. was three months old at this visit. *Id.* The pediatrician noted that A.S. was gagging on her bottle and she had decreased consumption of Similac. *Id.* It was also noted that A.S. had back arching. *Id.* The doctor observed a feeding and indicated "gagging at first but eventually was able to coordinate suck/swallow/breath." *Id.* A.S.'s weight was recorded as being in the tenth percentile. *Id.*

On April 17, 2012, A.S. returned for another pediatric visit. Ex. 8 at 5. The record noted "difficulty with feeding with tongue thrusting/top of mouth." *Id.* A.S. was in the tenth percentile for weight. *Id.*

On June 18, 2012, A.S. had her six-month pediatric visit. Ex. 8 at 4. A.S.'s weight was recorded as "↓3%." *Id.* Dr. Douglas noted that A.S. was sitting with support and was not consistently rolling over but had in the past. *Id.* A.S.'s mother reported that although A.S. had crossed her eyes before, this had become more noticeable since prior visits. *Id.* The doctor noted HEENT (head, eyes, ears, nose, and throat), EXTR, NEUR abnormalities, with additional

notations of "R eye medial gaze/poor tracking," "strabismus[6]," "↑ tone x 4 ext/feet + hands clenched," and "poor seated control/ ↓ upper body strength". *Id.* Dr. Douglas referred A.S. to ophthalmology and neurology for additional evaluation. A.S. received the DtaP, IPV, Hib, Hep. B, Prevnar, and RotaTeq vaccinations during this visit. *Id.* at 4, 15.

B. Post-Vaccination History

On June 19, 2012, Mrs. Svagdis called Preston Ridge Pediatric Associates. Ex. 8 at 3. The note states "parents went home and researched on internet and up all night processing." *Id.* Although they had an appointment at 9:00 that morning with Dr. Lipsky, Mrs. Svagdis indicated she was unable to get an appointment with Dr. Schuls, a neurologist, until August. *Id.* The transcriber noted "Mom requesting we call to get neurologist due to significant changes developmentally/neuro since 4 mo. will call [illegible] to attempt help with scheduling." *Id.*

On the same day, A.S. visited Dr. Steven Lipsky, an ophthalmologist, at the Thomas Eye Group. Ex. 8 at 17. Dr. Lipsky noted that A.S. "does not fix and follow well, but when she is attentive, she does follow." *Id.* Dr. Lipsky noted that A.S.'s eyes have crossed since birth. *Id.* Dr. Lipsky opined that he felt that "her developmental status is way behind and her vision may very well be appropriate for her developmental state." *Id.*

On June 20, 2012, A.S. visited Dr. Raymond Cheng, a neurologist at Child Neurology Associates, P.C. Ex. 3 at 1-2. Dr. Cheng stated A.S. presented with crossed eyes, lethargy, and stiffness. *Id.* at 1. Mrs. Svagdis informed Dr. Cheng that A.S. "always has both hands fisted," and "is always very stiff". *Id.* Dr. Cheng also noted that in the past few weeks, there has been a progressive worsening of the tendency to "zone out" and poor eye contact with parents when they are talking to A.S. *Id.* Petitioners also informed Dr. Cheng that A.S. had poor head control, especially when she was younger. Petitioners were also concerned "about failure to thrive because of dropping off the growth scale." *Id.* Dr. Cheng's neurological exam found:

> Bilateral poor eye contact. I was not able to get her attention and to engage. There is a persistent prominent ATNR (asymmetrical tonic neck reflex) response with fencing posturing. Cranial nerves show response to light, but no clear-cut focusing on face. Gag is intact. Face is symmetric. Motor examination shows diffusely increased tone in all four extremities with poor head control for her age. There is also bilateral scissoring when suspended vertically. The sensory exam is intact to pin and touch. Reflexes are also very brisk in all four extremities with upward going toes bilaterally. She was not able to really voluntarily reach for objects.

Id. at 2. Dr. Cheng's impression was that A.S. had "1. Spastic quadriplegia. 2. Suspected seizures/encephalopathy. 3. Global developmental delay. 4. Failure to thrive. 5. Question of possible etiology related to herpes. *Id.* Dr. Cheng directed A.S. to the emergency room to start an evaluation. *Id.*

[6] Strabismus is "an eye condition in which the visual axes cannot be directed at the same point of fixation under normal conditions of seeing." *Dorland's Illustrated Medical Dictionary*, (33 ed. 2019): https://www.dorlandsonline.com/dorland/definition?id= 47369 (hereinafter "Dorland's").

On the same day, A.S. went to the Children's Healthcare of Atlanta (CHOA) – Scottish Rite emergency room and was seen by Dr. Gregory Melnikoff. Ex. 11 at 2184. The History of Present Illness (HPI) section noted that

> Infant has been making unusual movements since birth including staring off into space, turning head to side and rigid extension of one arm, lasting approx. 20 seconds. Child has had problems with feeding since birth which has worsened over the last month. Child has only gained 4 ounces in the last month.

Id. at 2184-85. All review of systems were negative. *Id.* at 2185. A.S. was to undergo an EEG, MRI, labs, and subspecialty consultations. *Id.* at 2186.

The EEG performed on June 20, 2012 was "a normal awake and sleep EEG for age." Ex. 11 at 2280. The history taken at the time of the EEG noted that A.S. had been tracking up until five months of age and then began focusing less. *Id.* Her feedings had always been slow, "but over the past month, patient feedings have markedly decreased." *Id.*

Also on June 20, 2012, A.S. visited Dr. Barbara Bruce, a neurologist. Ex. 11 at 2192. Dr. Bruce noted that A.S.'s active problems included abnormal eye movements, abnormal involuntary movements, feeding difficulty in infant. **Consultation requested by Dr. Rowe for evaluation of developmental regression, possible seizures, and failure to thrive**." *Id.* (emphasis in original). The HPI provided additional details concerning A.S.'s development:

> It appears some concerns were raised ~2 months ago … pediatrician noted increased tone. Patient tends to keep arms flexed and hands in clenched positions (this has been going on for some time according to pictures mom has taken in the past). At 5 months patient began focusing on mom's face less. Patient has always had difficulty supporting self when parent is holding her on hip. Head control was better previously although it appears patient never had complete control. Three days ago, patient had 6 month vaccinations. Mom has noticed a significant regression in milestones since that time. Patient will not even focus on mom, her cooing has decreased as has her appetite (previously taking 3-4 ounces per meal and now taking < 2 ounces)… Patient is also more somnolent. Additionally patient has been experiencing paroxysmal events concerning for seizures. Patient will grimace and move her head/neck quickly back and forth. Patient also experiences episodes where she chews her tongue repetitively.

Id. at 2192-93. Dr. Bruce's impressions were that A.S. may have a metabolic/mitochondrial disorder, neurodegenerative disorder, and leukodystrophy. *Id.* at 2196.

On June 22, 2012, A.S. visited Dr. Willian Meyers, a gastroenterologist, for a consultation. Ex. 11 at 2186-87; 2188-92. Dr. Meyers noted, "No overt symptoms of reflex and normal anatomy on UGI today. Suspect feeding decline is a component of a yet to be diagnosed neurological, seizure, or metabolic disorder. Patient is at nutritional risk and may require long-term enteral access to meet her nutritional needs." *Id.* at 2186-87. A.S. was to be fed through a NG (nasogastric)

tube eight times per day. *Id*. at 2187. The video EEG performed on June 22-23, 2012 was normal. *Id.* at 2315. A.S. was discharged on June 26, 2012. *Id.* at 2173.

On June 29, 2012, A.S. was seen at by Dr. Bob Bagheri at Lakeside Pediatrics for "develop[mental] regression, hypertonia, bilat[eral] eye deviation, feeding prob. Esotropia."[7] Ex. 13 at 1, 5.

On July 9, 2012, A.S. visited Dr. Vaishali Kute at Chattahoochee Pediatrics with a chief complaint of "developmental regression post vaccines". Ex. 12 at 11. It was noted that A.S. had been admitted to the hospital for:

> possible seizures, pretty much non-responsive to any stimulation. Severe developmental regression. Had routine vaccines 2d before. Got NG tube 6/22/2012. Waiting on genetics tests results. She has made a lot of developmental progress since the hospitalization, but not 100%. She is now in ST and PT…. Congestion since birth. Would like ENT referral. Questions about GERD, she does not spit up, but she is on Zantac. Occasionally stomach acid will float up into her NG tube…. Eyes were crossing before the vaccines at 6mo WC.

Id. Dr. Kute's plan was "[a]wait report on labs ordered by geneticist. Continue PT, ST. Continue tube feeds, F/U with GI, neurology, genetics." *Id.* at 12.

On July 23, 2012, A.S. visited Dr. Kute for a weight recheck. Ex. 12 at 11. Dr. Kute noted that A.S. was having diarrhea multiple times per day that seems to have been resolved. *Id.* Dr. Kute's assessment was that A.S. has good weight gain and she was to continue her current feeding plan. *Id.*

On August 15, 2012, A.S. visited Dr. Kute for another weight recheck. Ex. 12 at 10. A.S. had continued feeding difficulties and had thrown up the morning of the appointment. *Id.* A.S. was to continue her current feeding plan and to follow up with "GI and genetics." *Id.*

On August 30, 2012, A.S. returned to Dr. Kute complaining of lactose intolerance. Ex. 12 at 9. Mrs. Svagdis reported that A.S. threw up after consuming yogurt and tried soy but continued to throw up. *Id.* Mrs. Svagdis also reported that A.S.'s bowel movements looked like tomato paste but when A.S. was switched to Goodstart, she threw up twice but had normal bowel movements. *Id*. Dr. Kute's assessment was, "GER [gastroesophageal reflux], good weight gain." *Id.*

On September 5, 2012, A.S. visited Dr. Kute for ear pulling and a cough. *Id.* at 8. Dr. Kute diagnosed A.S. as having an upper respiratory infection. *Id.* at 9.

On September 17, 2012, A.S. had a routine infant/child health check with Dr. Kute. Ex. 12 at 7-8. Dr. Kute noted that A.S. had gained enough weight such that her parents were trying to

[7] Esotropia is "strabismus in which there is manifest deviation of the visual axis of an eye toward that of the other eye, resulting in diplopia." Dorland's. https://www.dorlandsonline.com/dorland/definition?id=17375.

wean her off the feeding tube but A.S. was not tolerating solids well. *Id.* at 7. The records indicate that A.S. had more energy when she ate less. *Id.*

On October 9, 2012, A.S. visited Dr. Meyers for feeding concerns. Ex. 11 at 1582-84. Petitioners reported they were able to feed A.S. approximately six ounces with a NG tube consistently, but A.S. would pull at the tube, making feeding more difficult. *Id.* at 1583. Petitioners requested a gastrostomy tube ("G-tube") for more stable feeding. *Id.* Dr. Julie Glasson placed a gastrostomy tube on the same day. *Id.* at 1585-86.

On October 30, 2012, GeneDx analyzed A.S.'s buccal swab sample and prepared a genetic testing report. Ex 7 at 1-2. The testing revealed that A.S. had a NDUFA1 variant. *Id.* at 1. The report noted that "the clinical significance of this variant is unknown, although it is a strong candidate for a disease-causing mutation." *Id.*

On November 9, 2012, A.S. visited Dr. Bruce for possible seizures. Ex. 11 at 1235-37. The record noted that she is "currently having episodes where she has decreased responsiveness and after which it may take [A.S.] several minutes to "come to." She is also having episodes of sudden jerking of her arms and occasional head drop." *Id.* at 1235. A.S. was admitted for observation and an EEG. *Id.* at 1237. An EEG performed on the same day revealed "independent left and right occipital sharp waves. The discharges from the left occurred more frequently than the right…. This record was moderately abnormal given the presence of spikes from the bilateral occipital region." *Id.* at 1241-42.

On November 15, 2012, A.S. saw Dr. Fran Kendall of Virtual Medical Practice, LLC, with a chief complaint of a neurodegenerative course with loss of skills and onset of seizures, along with feeding issues. Ex. 10 at 6-9. Dr. Kendall specializes in metabolic, mitochondrial, and inherited genetics. Dr. Kendall "expressed considerable concern for the possibility of a Leigh disease picture." *Id.* at 8. Dr. Kendall recommended a follow-up in three months and asked that she be given access to the results of A.S.'s genetic testing. *Id.* at 8-9.

On December 12, 2012, A.S. underwent an EEG. Ex. 11 at 1115-16. The impression by the interpreting physician, Dr. Bryan Philbrook, was that this was "markedly abnormal" due to "1) a poorly developed background for chronological age; consistent with a diffuse encephalopathy. 2) Frequent posterior spikes and slow waves bilaterally. This record was consistent with localization related epilepsy and supports abnormalities in the posterior head regions." *Id.* at 1116.

On December 18, 2012, A.S. had an MRI, which was normal. Ex. 11 at 255.

On January 3, 2013, A.S. traveled to the Cleveland Clinic Neurological Institute Epilepsy Center and was admitted for observation. Ex. 5 at 9. Her history was taken by Dr. Julie Cernanec and detailed as:

> [A.S.] presents with developmental regression and drop attacks. Patient was born full term with no complications and has been developing normally until 6 months of age when she started having sudden regression of milestones after receiving her 6 month shots. No previous adverse reactions from 2 month or 4 month shots were

> noted. According to parents, within a few hours after receiving her 6 month[] shots, patient developed episodes of "stiffening" of both arms and legs; and was unable to roll and babble as she was previously able to do. She also had trouble with feeding, and per mom became as if she was a "newborn" again. They also noted that at this time, her eyes [were] crossing and so patient was seen by ophthalmology and neurology in Atlanta…. EEG and MRI brain also done which was allegedly normal…. She continued to have poor feeding and was NG fed for several months. She developed failure to thrive and G-tube was placed last October.
>
> In November, patient was noted to have episode of flexed posturing of the arms with blank gaze – EEG done which showed "optical seizures" and patient was started on trileptal. She did not improve on trileptal and in mid-December started having drop attacks. Parent provided a video which showed sudden flexed posturing of whole body. These episodes would occur around 4-5x a day usually in clusters and worse when waking up in the morning…. She is now having increasing frequency of drop attacks which prompted parents to get a second opinion at CCF [Cleveland Clinic Foundation].

Id. at 9. Dr. Cernanec suspected West syndrome, Lennox-Gastaut, or another neurometabolic disorder. *Id.* at 12.

A.S. visited Dr. Elaine Wyllie who performed a video EEG. *Id.* at 18. She noted a modified hypsarrhythmia pattern with multiregional and generalized sharp waves and generalized continuous slows. *Id.* at 20. During A.S.'s sleep, her EEG was discontinuous and several clusters of epileptic spasms were recorded. *Id.* There were also two instances of hypomotor seizures with arrest activity and eye deviation to the left. *Id.*

During her stay at the Cleveland Clinic, A.S. was also seen by Dr. Timothy Moss on January 4, 2013 for a medical genetics consult. Ex. 5 at 21. Dr. Moss informed Mr. Svagdis that "given the diagnosis of hypsarrhythmia, the number of potential causal genes is dramatically reduced, but still over 20. With that finding, more unlikely to be metabolic in nature, and the few metabolic causes have already been somewhat screened for." *Id.* Dr. Moss believed Rett and Rett-like syndromes were likely given A.S.'s regression but indicated the whole exome sequencing performed by GeneDx would have found something. *Id.* Dr. Moss encouraged Mr. Svagdis to communicate the hypsarrhythmia diagnosis to GeneDx for further analysis. *Id.*

Dr. Wyllie assessed A.S. again on January 5, 2013. Ex. 5 at 25-26. Dr. Wyllie discussed various treatment options with Petitioners, who chose to try Topamax for A.S.'s epilepsy. *Id.* at 25.

A.S. was discharged from the Cleveland Clinic on January 6, 2013 with instructions to consult with genetics, epilepsy, and neurology experts. Ex. 5 at 33.

On January 7, 2013, A.S. visited Dr. Robert Flamini at the Atlanta Headache Specialists & PANDA Neurology for a consultation. Ex. 2 at 26-29. Dr. Flamini's assessment noted infantile

spasms and developmental regression, "likely manifestation of severe underlying process yet to be labeled." *Id.* at 28.

On January 17, 2013, A.S. returned to CHOA for a "seizure disorder." Ex. 11 at 943-52. The medical records indicate that "Parents have not witnessed any clinical spasms for 'a while', but ha[ve] been noticing child 'crying out' which she previously would do prior to her clinical spasms. Continues on G-tube feeds and tolerating. No other concerns at present." *Id.* at 947. Another EEG was performed. *Id.* at 957. The impression from the EEG suggested global cortical dysfunction, consistent with a diffuse encephalopathy. *Id*.

On January 22, 2013, A.S. returned to Dr. Flamini for a follow-up visit. Ex. 2 at 22-25. The HPI noted that A.S. was starting to interact more with her parents and would sometimes reach and grab things. *Id.* at 22. A.S. was to continue her current medication and therapy and was recommended to undergo a longer EEG in the future. *Id.* at 24.

On February 11, 2013, A.S. and her parents had a genetic consultation with Dr. Vidya Krishnamurthy, who diagnosed A.S. with a mitochondrial metabolism disorder. Ex. 7 at 60-61. Dr. Krishnamurthy informed Petitioners that a variant of the NDUFA1 gene could cause a complex 1 deficiency and recommended Mrs. Svagdis get genetic testing done, as the gene was on the X chromosome. *Id.* at 60. The records indicate that a buccal swab was done with Dr. Goldenthal which revealed a complex IV deficiency but required retesting. *Id.*

On February 26, 2013, A.S returned to Dr. Flamini for a follow-up. Ex. 2 at 19-21. A.S. was no longer experiencing spasms or hypsarrhythmia. Petitioners informed Dr. Flamini that A.S. continued to stare off several times per day but had been more attentive to noises and changes. *Id.* at 19.

On March 6, 2013, A.S. returned to Dr. Kendall for a follow-up appointment. Ex. 10 at 2-5. Dr. Kendall discussed A.S.'s genetic testing results with Petitioners, and informed them that while she believed A.S. had mitochondrial disease, she could not "classify her as a Leigh disease patient given her brain MRI findings although she is very Leigh-like in regards to her significant encephalomyopathic findings." *Id.* at 4. Dr. Kendall recommended that A.S. undergo another swallow study and undergo additional seizure disorder testing. *Id.*

On April 3, 2013, A.S. underwent a video EEG at PANDA Neurology. Ex. 2 at 36. The study was abnormal due to "the presence of a persistent area of focal abnormality over the left posterior quadrant. There are no clear epileptiform components associated with it." *Id.*

On April 23, 2013, A.S. returned to PANDA Neurology for a follow-up. Ex. 2 at 16-18. Dr. Flamini noted that Dr. Kendall diagnosed A.S. with a mitochondrial disorder. *Id.* at 16. A.S. was to continue her topiramate medication and therapy. *Id.* at 18.

On August 2, 2013, A.S. returned to Dr. Flamini for a follow-up. Ex. 2 at 13-15. Dr. Flamini noted no further regression and slow progression. *Id.* at 16. A.S. was able to hit toys and touch objects on command and was able to roll, but was still unable to sit independently. *Id.*

On August 8, 2013, A.S. underwent another EEG at PANDA Neurology. Ex. 2 at 35. The EEG was abnormal due to "poorly developed background for chronological age with diffuse slowing. However, interpretation is limited by continuous myogenic artifact." *Id.*

On August 21, 2013, A.S. returned to the Cleveland Clinic to see Dr. Parikh. Ex. 5 at 190-95. Dr. Parikh's impression noted that A.S. worsened on Trileptal but improved on TPM, which raised questions concerning an underlying sodium channelopathy. Dr. Parikh also suggested A.S. may have an underlying mitochondrial disorder because of A.S's slight elevation in lactate levels. *Id.* Dr. Parikh stated he could not exclude an inflammatory etiology or an underlying onset epileptic encephalopathy condition. *Id.* He recommended additional genetic testing. *Id.* at 195.

On November 4, 2013, A.S. saw Dr. Flamini for a follow-up. Ex. 2 at 10-12. A.S. was able to sit by herself with no support for up to a minute and was able to bring food to her mouth. *Id.* at 10.

On November 14, 2013, A.S. underwent a 24-hour ambulatory EEG at PANDA Neurology. Ex. 2 at 34. The EEG recorded interictal abnormalities including diffusion background slowing and a "single well-delineated right frontotemporal (F8/T4) spike and slow wave." *Id.* Dr. Flamini noted that clinical and neuroimaging correlation was necessary. *Id.*

On February 5, 2014, A.S. returned to see Dr. Flamini for a follow-up appointment. Ex. 2 at 7-9. Dr. Flamini noted that the potential mitochondrial disorder had no confirmatory findings. *Id.* at 7. A.S. was able to use her hands and had been tested for Retts and atypical Retts. *Id.* A.S. also had normal MTHF (5-Methyltetrahydrofolate) in her CSF. *Id.* He also noted that A.S. had not experienced any clinical seizures since January 2013. *Id.*

On April 30, 2014, A.S. returned to the Cleveland Clinic to see Dr. Parikh. Ex. 5 at 217-20, 236. Exome genetic testing performed at the prior visit revealed "no disease-causing mutation." *Id.* at 218. The records indicate that A.S. was clinically stable and that her general health was good. *Id.* at 219.

On May 14, 2014, A.S. returned to Dr. Flamini. Ex. 2 at 4-6. Dr. Flamini noted A.S was making progress: she was able to grab objects, play more, maintained better eye contact, and could sit by herself. *Id.* at 4. The underlying diagnosis was still unknown however a genetic disorder was still being considered. *Id.*

On June 5, 2014, A.S. visited Shriners Hospitals for Children for right hip dysplasia. Ex. 6 at 1-5. A.S. had rolled off a bed and onto the floor and was uncontrollably crying the next day.

On August 14, 2014, A.S. had a follow-up appointment with Dr. Flamini. Ex. 2 at 1-3. The HPI noted:

> [A.S.] returns in f/u today with remote h/o infantile spasms controlled for the last 20 months, appearing at age 11m and present for only one month which responded to Topamax. The etiology is still unclear, has seen several physicians and has been seen for an opinion at the Cleveland Clinic Dr. Parik [sic], who did not consider[]

> her to have a mitochondrial d/o and did not feel the NDUFA gene [] is responsible [either]…. She continues to make slow developmental gains tested at ~10 months overall. Makes noises, still won't swallow and is tube fed. Motor skills including sitting independently with lateral protective reflects, not up on all 4's. Grabbing things quicker PT OT ST and Vision therapy as well as massage therapy.

Id. at 1. A.S. was to continue medication and therapy. *Id.* at 3.

III. Petitioners' Affidavits and Testimony

A. Affidavits of Jeremy and Kimberly Svagdis

The affidavits filed by both Petitioners are identical and will be summarized as one. Exs. 1, 14. A.S. received her vaccinations at the Forsyth County Health Department on June 18, 2012. *Id.* at 1. According to Petitioners, the same day, A.S. became stiff and unresponsive to stimuli, and was completely "out of it." *Id.* Mrs. Svagdis called A.S.'s pediatrician and left a message to report these symptoms on June 19, 2012. *Id.* at 2. A.S. visited Dr. Raymond Cheng on June 20, 2012 who diagnosed her with "spastic quadriplegia and suspected seizures and encephalopathy, among other things" and referred A.S. to Children's Healthcare of Atlanta – Scottish Rite for further work up. *Id.*

At CHOA, testing was inconclusive and A.S. was discharged on June 26, 2012 with a working diagnosis of "abnormal eye movements, abnormal involuntary movements, and feeding difficulty." Exs. 1, 14 at 2-3. A.S. was then placed on a G-tube on October 9, 2012. *Id.* at 3. On January 9, 2013, Petitioners took A.S. to the Cleveland Clinic for an evaluation of her neurologic function and overall functional decline. *Id.* A.S. had medically refractory seizures since seven months of age with epileptic spasms beginning in December 2012, and was ultimately diagnosed as having infantile spasms and developmental regression. *Id.*

A.S. returned to the Cleveland Clinic on August 21, 2013 and visited Dr. Sumit Parikh. Exs. 1, 14 at 3. Dr. Parikh was "unable to exclude an inflammatory etiology as a cause of her symptoms" and the "onset of epilepsy shortly thereafter raises question of an underlying infantile onset epileptic encephalopathy condition as well." *Id.* at 3-4. According to Petitioners, there were concerns of a mitochondrial disorder that have since been ruled out by her current treating physicians. *Id.* at 4.

B. Testimony

1. Kimberly Svagdis

Mrs. Svagdis testified that she was a stay-at-home mother with A.S., and her one-year-old sister, M.S. Tr. at 6-7. A.S. was seven years old at the time of the entitlement hearing but has remained developmentally at around the age of six to ten months. *Id.* at 8. A.S. requires 24-hour care, wheelchair assistance, and still feeds via feeding tube. *Id.* A.S. goes to school but has a one-on-one nurse to take care of her needs. *Id.* at 11.

A.S. continues to see many doctors and goes to physical therapy twice per week. Tr. at 13-14. A.S. continues to have absence seizures, where she will get quiet and stare off into the distance, and not move. *Id.* at 18. Mrs. Svagdis stated these seizures occur every night and sometimes during the day. *Id.* at 19-20. A.S. has been on a number of anti-seizure medications in the past but is now only on Fycompa. *Id.* at 18, 20.

A.S. received her six-month vaccinations at the Forsyth Community Health Center because Mr. Svagdis was self-employed at the time and thus the family had no health insurance. Tr. at 23. Prior to her vaccinations, A.S. had her six-month well child visit with Dr. Elinor Douglas. *Id.* at 25. Mrs. Svagdis informed Dr. Douglas that A.S. crossed her eyes, but Mrs. Svagdis also had a crossed eye so she wasn't concerned. *Id.* Mrs. Svagdis also clarified that A.S. had consistently been able to roll over, and has video of A.S. rolling over, although it was noted as inconsistent in the medical records. *Id.* at 27. Mrs. Svagdis remembered leaving the six-month appointment confused because A.S. was referred to see an ophthalmologist and neurologist. *Id.* at 31. As a result, Mrs. Svagdis did some research online because she noticed A.S. was clenching more, continued to have feeding problems, and have more severe eye crossing. She decided to call back the following morning to get clarification and "get this going." *Id.* at 34.

Between June 18, 2012 and June 20, 2012, Mrs. Svagdis noticed that A.S. was less engaging and would become really quiet. Tr. at 40. Mrs. Svagdis stated that on June 19, 2012, she continued to worry about A.S. and search online but was able to schedule an appointment with Dr. Cheng the next day with help from Dr. Douglas's office. *Id.* at 37-38. Mrs. Svagdis remembered that during the appointment with Dr. Cheng, he "pointed out the hospital across the street and told us to go there," so they went to the Children's Hospital of Atlanta ER. *Id.* at 39, 41. A.S. was immediately given an EEG and was admitted to the hospital for the next six days. *Id.* Mrs. Svagdis testified that prior to June 18, 2012, A.S. never had issues with tracking objects and that she had not heard of the terms "spastic quadriplegia" or "suspected seizures, encephalopathy," or that A.S. was developmentally delayed. *Id.* at 44-46. Mrs. Svagdis stated that A.S.'s current issues include global developmental delays, strabismus, mitochondrial disease/dysfunction (which some doctors have diagnosed her with and some haven't), epilepsy, feeding difficulties, incontinence, and hip dysplasia. *Id.* at 67-68.

2. Jeremy Svagdis

Mr. Svagdis works as a telecom project manager, which involves upgrading cell phone towers. Tr. at 71. Mr. Svagdis testified that he was the secondary caregiver to A.S. He testified that Mrs. Svagdis stayed home to take care of A.S. and M.S. but he attempted to go to doctor appointments with A.S. *Id.* at 71-72. Mr. Svagdis testified that he did not remember attending the April 17th wellness visit but did attend the June 18th appointment. *Id.* at 72-73. Mr. Svagdis recalled becoming concerned because A.S. repeatedly shook her head back and forth horizontally on June 19, 2012. *Id.* at 76-77. Mr. Svagdis further testified that the head shaking occurred prior to the visit with Dr. Lipsky on June 19, 2012 and that the appointment was not significant. *Id.* at 77-78. However, the appointment with Dr. Cheng, the following day was significant because Dr. Cheng instructed them to go to the hospital across the street. *Id.* at 79. Mr. Svagdis testified there was a rapid decline in A.S. between June 18, 2012 and June 26, 2012, which included the head shaking, lack of eye contact and interaction. *Id.* at 81-82, 84.

IV. Expert Opinions and Qualifications

A. Petitioners' Expert: Dr. Marcel Kinsbourne

1. Qualifications

Dr. Kinsbourne received his medical degree from Oxford University in 1955. Ex. 18 at 1 (hereinafter "Kinsbourne CV"). Dr. Kinsbourne completed post-doctoral training in neurology and pediatrics and is board certified in pediatrics. Kinsbourne CV at 1. Dr. Kinsbourne has held a number of hospital and academic appointments. *Id.* at 2. He serves on numerous editorial boards, including Brain Research, Cognitive Neuropsychiatry, Journal of Psycholinguistic Research, and many others. *Id.* at 5. Dr. Kinsbourne is also part of a number of professional societies. *Id.* at 5-6. Dr. Kinsbourne has published over 400 articles and books regarding pediatrics and neurology. *See id.* at 7-40. Dr. Kinsbourne has not seen patients in approximately 30 years. *See Berg v. Sec'y Health & Hum. Servs.*, No. 16-650V, 2021 WL 6883495 (Fed. Cl. Spec. Mstr. Dec. 14, 2021) (discussing Dr. Kinsbourne's qualifications); *Ellis v. Sec'y of Health & Hum. Servs.*, No. 13-336V, 2018 WL 4846547, at *25 (Fed. Cl. Spec. Mstr. Sept. 6, 2018) (same).

2. Expert Report

Dr. Kinsbourne relied on Dr. Boles' expertise as a geneticist and mitochondrial specialist as well as his expert report (Ex. 30) highlighting A.S.'s illness as consistent with a mitochondrial disorder. Ex. 17 at 4 (hereinafter "First Kinsboune Rep."). Dr. Kinsbourne based his report on the "neurological implication of the diagnosis of a mitochondrial disorder as they apply in the case of [A.S.]." *Id.* Dr. Kinsbourne also admitted that A.S. has never been given a definitive diagnosis by treating physicians though a mitochondrial disorder has been suggested numerous times. *See id*.

Regarding his proposed mechanism, Dr. Kinsbourne stated "Infections and vaccinations can trigger the production of proinflammatory cytokines such as TNF-alpha, IL-6 and IL-1 beta. These agents in turn can cause the synthesis of reactive oxygen species (ROS) and thereby generate oxidative stress." *Id.* at 5. Oxidative stress can impair the role of mitochondria in energy production, and can cause cell damage and cell death. *Id.* Dr. Kinsbourne stated "the acellular pertussis vaccine and other vaccines activate the Toll-like receptors of the innate immune system, leading to the release of proinflammatory cytokines." He further stated that "the onset of [A.S.'s] epileptic encephalopathy was abrupt, within hours of her vaccinations." *Id.* at 6 Such brief intervals are typical for pertussis vaccine encephalopathies. Thus, the onset of [A.S.]'s encephalopathy occurred within a medically reasonable temporal interval after the vaccinations." *Id.*

3. Testimony

Dr. Kinsbourne provided testimony on September 5, 2019. I recognized Dr. Kinsbourne as an expert in neurology. Tr. at 160. He stated that his opinion does not necessarily rely on the presence of mitochondrial dysfunction in A.S. but that the vaccinations A.S. received on June 18, 2012 triggered a "very abrupt, unexpected regression of function in A.S." *Id.* at 161. Dr.

Kinsbourne deferred to Dr. Boles regarding whether mitochondrial dysfunction played a role in A.S.'s condition. *Id.* at 162.

Dr. Kinsbourne testified that there was no evidence of epilepsy at the onset of the vaccine injury but brain damage did occur which resulted in the later onset of infantile spams and seizures. Tr. at 163. On the day of A.S.'s vaccinations, it was documented that A.S. required assistance to sit up and was not consistently rolling over. *Id.* at 170; Ex. 8 at 4. Dr. Kinsbourne stated that this indicated that "something is going wrong neurologically" and that per Dr. Boles' mitochondrial dysfunction theory, "the mitochondria are showing signs of splaying." He testified that this shows the vaccinations significantly aggravated a pre-existing condition. *Id.* at 170.

Dr. Kinsbourne clarified that the vaccination "cause[d] a scenario which made infantile spasms more likely to happen.", specifically that neuro intra-brain damage or encephalopathy occurred in June and that over the next few months, A.S. developed infantile spasms. Tr. at 175-76. The fact that A.S. had spastic quadriplegia on June 20, 2012 when Dr. Cheng examined her is evidence of acute brain injury. *Id.* at 176-77.

Dr. Kinsbourne also opined that if A.S. did not have a mitochondrial disorder, he still believed the vaccinations could have caused her injury. Tr. at 187.

4. Post-Hearing Opinion

Dr. Kinsbourne filed a post-hearing statement (Ex. 59) (hereinafter "Second Kinsbourne Rep.") and a supplemental report (Ex. 64) (hereinafter "Third Kinsbourne Rep.").

Dr. Kinsbourne's post-hearing statement addressed A.S.'s MRI and EEGs and how they did not reveal any acute changes post-vaccination. Dr. Kinsbourne stated that because A.S. had a mitochondrial or metabolic encephalopathy, there was no structural damage, trauma, or anoxia that would have appeared on A.S.'s brain imaging. Second Kinsbourne Rep. at 1. Cytokine mediated dysfunction would not necessarily result in widespread death of neurons but instead a "functional" decline, where affected neurons underperform. *Id.* According to Dr. Kinsbourne, it would take a long time for neurons to deteriorate to the extent they become visible on an MRI, but they could be visible on more sensitive neuroimaging such as proton magnetic spectroscopy (MRS). *Id.* Dr. Kinsbourne added that diagnostic criteria for mitochondrial dysfunction do not require an abnormal MRI but are based on metabolic, genetic and histological studies. *Id.*

Dr. Kinsbourne's supplemental report rebutted Drs. McCandless and Wiznitzer's supplemental reports (Exs. R and S). Dr. Kinsbourne specifically disagreed with Dr. Wiznitzer's Gropman article, arguing severity of change observed on MRI in mitochondrial patients is not reflected in clinical practice; patients with severe mitochondrial disorders may have completely normal brain imaging. Third Kinsbourne Rep. at 1. Neuroimaging in children is also difficult to read/define. *Id.* Dr. Kinsbourne cited to the Mitochondrial Medicine Society, which included the following as diagnostic criteria: biochemical tests in blood, urine and spinal fluid; DNA testing, pathology and biochemical testing of tissues, and neuroimaging. *Id.* at 2; *citing* Parikh et al., *Diagnosis and management of mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society*, 17 GENET MED. 9, 698-701 (2015) (filed as Ex. 61). On the

neuroimaging criteria, the MMS states that "Neuroimaging cannot by itself be the absolute criterion for disease confirmation." *Id.*

B. Petitioners' Expert: Dr. Richard Boles

Dr. Boles provided one expert report in this case and testified at the entitlement hearing.

1. Qualifications

Dr. Boles received his medical degree from UCLA in 1987. Ex. 31 (Boles CV) at 1. At the time of the entitlement hearing, Dr. Boles was board certified in clinical biochemical genetics but had previously been board certified in pediatrics and clinical genetics. Tr. at 88-89. Dr. Boles taught at the Keck School of Medicine at the University of Southern California from 1993-2014 in both clinical pediatrics and pediatrics. Boles CV at 2. Dr. Boles also serves as the Director of Genetics Research, Director of CCS Metabolic and Mitochondrial Disease Center, and Director of Newborn Screening Program at the Children's Hospital Los Angeles Medical Genetics. *Id.* at 3. Dr. Boles has actively participated in research in the last ten years and has two patents. *Id.* at 6-7. Dr. Boles has published 74 peer-reviewed articles, seven book chapters, and has been invited to lecture both nationally and internationally. *See id.* at 8-13, 20-21, 21-23. I recognized Dr. Boles as an expert in genetics and mitochondrial medicine. Tr. at 97.

2. Expert Report

Dr. Boles provided a summary of mitochondrial dysfunction and his experience in the field. Ex. 30 (hereinafter "Boles Rep.") at 1-3. Dr. Boles also provided a medical summary of A.S.'s health since birth. *Id.* at 3-8.

Dr. Boles asserted that A.S.'s physicians believe her developmental regression began after June 18, 2012. Boles Rep. at 8. Dr. Boles did not cite to any specific records but stated there was "excellent contemporaneous documentation" and that "substantial neurodevelopmental issues were noted within hours of vaccination." He further noted that "[A.S.] was recorded to have had an acute loss of all milestones, going from an essentially-normal 6-month old infant to the developmental status of a newborn." *Id.*

Regarding A.S.'s underlying condition, Dr. Boles stated that "multiple aspects of [A.S.]'s case are consistent with the presence of an underlying mitochondrial dysfunction." Boles Rep at 8. These signs include: mild neurological findings noted on the day of the third set of vaccinations, or a mild neurological disease preceded that vaccination; acute developmental regression; seizures, infantile spasms, central hypotonia, spastic quadriplegia, and hip dysplasia; gastrointestinal dysmobility; a negative family history of autosomal recessive diseases. *Id.* at 8-9.

Dr. Boles conceded that there is "no primary (exact, underlying) molecular (DNA-based) diagnosis in [A.S.]," however "only 25-50% of patients with mitochondrial dysfunction receive an exact molecular diagnosis." Boles Rep at 11. Dr. Boles additionally stated that "the precise mechanism of vaccine-associated injury in [A.S.] is not clear at the present time, but likely involves immune-regulated processes," and "the general model is that a small subset of children are

genetically susceptible." *Id.* Finally, Dr. Boles concluded, "since [A.S.]'s developmental regression occurred shortly following vaccination, causality between her disease and the vaccination are highly likely… It is my opinion that, to a reasonable degree of probability, that a large degree of [A.S.]'s disease is vaccine related." *Id.*

3. Testimony

Dr. Boles provided testimony regarding the function of mitochondria in a cell, its discovery, and its importance to research as mitochondrial dysfunction "underlies a very large amount of disease". Tr. at 97-98. Dr. Boles then discussed how he would diagnose mitochondrial dysfunction in children. *Id.* at 99-101.

Signs of mitochondrial dysfunction as it relates to A.S. include global development delay, epilepsy, loss of milestones or regression, and GI disease. Tr. at 101-02. A.S.'s need for a feeding tube is another sign of mitochondrial dysfunction, as is obstipation, defined by Dr. Boles as bowels that are not moving at all. *Id.* at 103.

Dr. Boles noted that A.S.'s plasma lactate was mildly elevated three times in June 2012. *Id.* at 106. One elevated reading is normally not a concern however it is "consistent with mitochondrial dysfunction and suggestive thereof, but not highly specific." *Id.* at 108. The lactate levels are a part of a "constellation" of symptoms that may not be highly specific but in combination are "highly specific for mitochondrial dysfunction." *Id.* at 109. So additional to the lactate levels, A.S.'s pyruvate, succinate, citrate, and glutarate levels were mildly or extremely elevated. *Id.* at 109-12. These compounds are involved in the Krebs cycle, which is an important cycle in the center of metabolic pathways, and important to make energy in cells. *Id.* at 111.

Dr. Boles additionally identified citrate synthase as "a very good indicator of mitochondrial dysfunction." Tr. at 114. Specifically, Dr. Boles stated that A.S.'s citrate synthase levels were 340% above normal; when levels are elevated, a patient usually has mitochondrial dysfunction and when it's over 200%, it's very highly indicative. *Id.*

Dr. Boles additionally stated that A.S. had a buccal swab test in 2012 which was abnormal, and further demonstrated mitochondrial dysfunction. Tr. at 115-16. The buccal swab tested for methyltetrahydrofolate, which is low in the case of mitochondrial dysfunction. *Id.* at 121. The buccal swab testing confirmed Dr. Boles' "clinical suspicion of mitochondrial dysfunction." *Id.* at 120.

Dr. Boles also discussed his interpretation of the Haas article and how his understanding of the "red flags" of a mitochondrial disorder differ from the views of Dr. McCandless. Tr. at 123. Encephalopathy is one of the red flags. *See* Haas et al., *Mitochondrial Disease: A Practical Approach for Primary Care Physicians,* PEDIATRICS, 1326-33 (2007) (filed as Ex. K, Tab 2) (hereinafter "Haas"). Dr. Boles noted that "in my mind, [A.S.] has encephalopathy. There is neurodegeneration. Again, this patient has neurodegeneration." *Id.* Dr. Boles also stated that another red flag is "severe dysmotility…and this patient has severe dysmotility." *Id.* at 123-24. Dr. Boles acknowledged that he could not definitely say that other red flags were present in A.S.'s case, but "the question is, how many red flags do you happen to have before it's suspicious for

mitochondrial dysfunction." *Id.* at 124. Ultimately, Dr. Boles concluded that the constellation of findings, including Krebs cycle intermediates, indicate A.S. has mitochondrial dysfunction "at more than the 50% level." *Id.* at 122, 124-25. A.S.'s previous differential diagnoses included Kearns-Sayre syndrome and Leigh-like syndrome, both of which are mitochondrial diseases, which are a subset of mitochondrial dysfunction. *Id.* at 127. In further support of his point, Dr. Boles also noted that Dr. Kendall's buccal swab studies were noted for signs of mito-proliferation and complex IV deficiency, which is also consistent with mitochondrial dysfunction. *Id.* at 129-30.

Regarding the NDUFA1 gene, Dr. Boles stated that at the time (2013) it was considered to be related to disease, but over time it was discovered that the gene was too common and not disease linked, so it would be interpreted as a benign variant today. Tr. at 131.

Dr. Boles also testified that it is unclear when A.S.'s mitochondrial dysfunction began, stating that "it's unclear to say whether [symptoms] were present between the four and six-month visit and they developed at some point at that time or that they had just developed in the couple hours or so since the vaccination." Tr. at 137. He further testified, "What we do know is that at four months, she had a normal evaluation, and at six months, she had a mildly abnormal evaluation." *Id.*

C. Petitioners' Expert: Dr. M. Eric Gershwin

Dr. Gershwin provided one expert report in this case (Ex. 37, hereinafter "Gershwin Rep.") and also testified during the entitlement hearing.

1. Qualifications

Dr. Gershwin received his medical degree from Stanford University in 1971 and is board certified in internal medicine, rheumatology, and allergy and clinical immunology. Ex. 38 (Gershwin CV) at 1-2. He is currently the Jack and Donald Chia Professor of Medicine and a Distinguished Professor of Medicine the University of California, Davis. *Id.* at 2. Dr. Gershwin has won numerous awards including a Doctor of Philosophy Honoris Causa from the University of Athens, for his contribution in immunology and medicine, and is the Professor Henry N. Neufeld Memorial Award from the United States-Israel Binational Science Foundation in 2014. *Id.* at 1. Dr. Gershwin has ten patents and serves as the editor-in-chief for Clinical Reviews in Allergy, Reviews in Autoimmunity, Autoimmunity Reviews, and Journal of Autoimmunity, as well as an ad hoc editor for numerous other publications. *See id.* at 5-7. Dr. Gershwin has published more than 900 papers, 162 book chapters, and 69 books/monographs. *See id.* at 8-12, 13-91, 92-106.

2. Expert Report

Dr. Gershwin stated that his medical opinion was based on the assumption that A.S. suffered from a genetic mitochondrial defect, because he agreed with Dr. McCusker "that under normal circumstances there would not be expected to be an abnormal increase of cytokines following vaccination." Ex. 37 at 2 (hereinafter "Gershwin Rep."). Because of A.S.'s genetic mitochondrial defect, "[A.S.] would be more susceptible to cytokine production than a normal

child who does not have mitochondrial dysfunction." *Id.* Because of mitochondrial dysfunction, there are changes in ATP production, reactive oxygen species, calcium dysregulation, and mitochondrial DNA damage that would make A.S.'s brain more susceptible to damage. *Id.*

3. Testimony

I recognized Dr. Gershwin as an expert in the field of immunology. Tr. at 199. Dr. Gershwin testified that his opinion was "entirely dependent" on A.S. having a mitochondrial defect or dysfunction. Tr. at 200-01. When a person is vaccinated, cytokines are produced as a part of the innate immune response. *Id.* at 201. Cytokines can cross the blood-brain barrier (BBB) and some are produced in the brain as well and will result in oxidative stress. *Id.* at 202. Oxidative stress is a "noxious type of stimulation," that "could be as simple as eating too much fat in your diet. It releases … super-ions that punch holes in cells." *Id.* Cytokines interact with mitochondria in an inflammatory environment. *Id.* Mitochondrial DNA is susceptible to oxidative stress which creates DAMPS (danger associated molecular patterns), which lead to cell death through apoptosis or autophagy. *Id.* at 203. Specifically, "[w]hen the mitochondrial DNA is stressed, it's not healthy for cells and the cells will die or they don't produce as much energy and that makes the cell dysfunctional… and the lower the amount of energy, the more dysfunctional it becomes." *Id.* at 204.

Dr. Gershwin stated that there were approximately 18 different antigens within the vaccines that A.S. received. Tr. at 205-06. Those antigens released cytokines relatively quickly because she had received two sets of vaccinations prior to her six-month vaccinations. *Id.* at 206. Dr. Gershwin added that "her mitochondria are considered like a sponge [which] is abnormal. The sponge will bend and flex and stress the mitochondrial DNA which is in it… that reduces the amount of viable energy for that cell and the cell will be stressed and will die." *Id.* Additionally, "the more times you're immunized, the higher the vaccine response will be." *Id.* at 206-07. Dr. Gershwin testified that interleukin-1 (IL-1) is a cytokine that is more likely to cross the BBB. *Id.* at 208.

Dr. Gershwin confirmed that he agreed "with virtually everything Dr. McCusker wrote in her report" and that it was a very learned and scholarly report but they "differ about the target organ[elle]". Tr. at 214. Dr. Gershwin further testified that he believes A.S. had an anoxic injury in the brain from the vaccinations. *Id.* at 216. A.S developed cytokines as any other normal person or toddler would post-vaccination, it was her mitochondria that could not handle the cytokines the same way a healthy person would. *Id.* at 218. As a result, A.S.'s mitochondria became more dysfunctional and produced less energy affecting the neurological system. *Id.* Unlike other parts of the body, the brain does not have the ability to repair itself. *Id.* at 218-19. This leads to a "vicious cycle" of mitochondrial DNA becoming damaged and releasing DAMPs and cells dying. *Id.* at 219.

A.S. having developmental delay before her six-month vaccinations gave us a clue that "something [was] wrong with her to begin with" and the vaccines were an accelerator, or a "trigger to the falling off the cliff." Tr. at 224. Inherent in Dr. Gershwin's proposed mechanism is that A.S. had developmental issues prior to the vaccines and the vaccines produced oxidants that affected her mitochondrial DNA and worsened her underlying condition. *Id.* at 225.

D. Respondent's Expert: Dr. Max Wiznitzer

1. Qualifications

Dr. Wiznitzer received his medical degree from Northwestern University in 1977 and completed a fellowship in developmental disorders and pediatric neurology. Ex. B (hereinafter "Wiznitzer CV") at 1. Dr. Wiznitzer is currently an associate professor of neurology, associate professor of international health, and professor of pediatrics at Case Western Reserve University. Wiznitzer CV at 2. Dr. Wiznitzer is board certified in neurology with special qualification in child neurology, neurodevelopmental disabilities, and pediatrics. *Id.* at 5. Dr. Wiznitzer has written more than 60 papers, 11 book chapters, and 55 abstracts. *Id.* at 13-24.

2. Expert Reports

Dr. Wiznitzer submitted four expert reports in this case. Ex. A (hereinafter "First Wiznitzer Rep."), Ex. I (hereinafter "Second Wiznitzer Rep."), Ex. N (hereinafter "Third Wiznitzer Rep."), and Ex. R (hereinafter "Fourth Wiznitzer Rep."). Dr. Wiznitzer opined that A.S.'s history of difficulties with feeding and her neurological examination on June 18, 2012 were not subtle neurological problems but were representative of A.S.'s change in neurologic function. First Wiznitzer Rep. at 18. It is Dr. Witznitzer's opinion that Mrs. Svagdis' phone call to Dr. Douglas on June 19, 2012 was to discuss the well-child visit the previous day because the notes do not report change in mental status, nor do the ophthalmology visits on June 19, 2012 and the neurology visit on June 20, 2012 with Dr. Cheng. *Id.* When A.S. was admitted to CHOA, the EEG was normal and A.S. was awake and alert. *Id.* According to Dr. Wiznitzer, A.S. had no acute deterioration and when A.S. was properly fed, she showed improvement. *Id.* at 19.

Dr. Wiznitzer stated that "Dr. Kinsbourne's hypothesis of a cytokine related injury to the brain due to the effect of cytokines on mitochondria has no biologic plausibility." First Wiznitzer Rep. at 19. Dr. Kinsbourne relied on one article (Ex. 22), which involved an in vitro model of microglia activation by lipopolysaccharide (LPS – which was not present in the vaccines given to A.S.). Furthermore, there is no evidence of cytokines crossing the BBB or that A.S. had any brain injuries, demonstrated by the MRIs taken in 2012, or that A.S.'s microglia were activated. *Id.* Dr. Wiznitzer also disagreed with Dr. Kinsbourne's opinion that A.S. had epileptic encephalopathy within hours of her June 18, 2012 vaccinations. *Id.* Dr. Wiznitzer stated that A.S. had no evidence of any seizure activity until months after her allegedly causal vaccines and a video EEG performed in June recorded paroxysmal events that were not epileptic in nature. *Id.* It is Dr. Wiznitzer's opinion that A.S. had a history of developmental regression that predated vaccination and did not have an acute worsening after her June 18, 2012 vaccines.

In his second report, Dr. Wiznitzer refuted Dr. Gershwin's medical literature and how it related to A.S. in particular. *See generally* Second Wiznitzer Rep. Dr. Wiznitzer opined that Dr. Gershwin's conclusions are not supported by the contemporaneous medical records or his cited medical literature. *Id.* at 3.

3. Testimony

I recognized Dr. Wiznitzer as an expert in pediatrics, pediatric neurology, and neurodevelopmental disabilities. Tr. at 256. Dr. Wiznitzer testified that after listening to Petitioners' testimony, his opinion remained unchanged. Tr. at 258. He testified that A.S. had significant neurologic dysfunction predating her June 18, 2012 vaccinations and she followed the clinical course expected from her underlying neurologic condition. Tr. at 258. At A.S.'s four-month wellness check, her parents reported difficulty feeding, which is a neurologic issue. A.S. specifically had issues sucking and swallowing. *Id.* at 260. A.S. was also thrusting her tongue, which indicated lack of coordination in oral motor movements. *Id.* at 261. A.S. showed ongoing feeding problems. She was born in the 50th percentile for weight, dropped to the 10th percentile around two-and-a-half months, and dropped to the 3rd percentile at six months of age. *Id.* at 264. This indicated a long-standing issue with obtaining adequate calories to grow. *Id.* A.S.'s eye crossing also demonstrated less brain control, since eye movement is controlled by the brain. *Id.* at 265.

Dr. Wiznitzer also discussed A.S.'s lack of tone, inability to sit without support, and feet/hand clenching as concerns. *Id.* at 267. On June 20, 2012, A.S. was noted to have spastic quadriplegia, which is a form of increased tone. Dr. Wiznitzer testified that "[s]pasticity is never an acute reaction to a brain stressor." *Id.* at 267-68. He made this point by discussing adult stroke patients, who initially have low tone in the affected body parts and then two weeks later present with spasticity. *Id.* at 268.

Dr. Wiznitzer reviewed the medical records from A.S.'s visit with Dr. Cheng on June 20, 2012. Tr. at 273-79. A.S. had a persistent ATNR (asymmetric tonic neck reflex), which is present in all children at birth until about four months of age. A child cannot develop good reaching or grabbing until the ATNR disappears since it is an unvoluntary movement of the arm when one's head turns. *Id.* at 274. A child also cannot roll well with the ATNR intact. *Id.* Dr. Cheng also documented that Petitioners reported A.S. had been zoning out more over the past few weeks; she exhibited poor eye contact and poor head control. *Id.* at 275. Dr. Wiznitzer believed that Dr. Cheng was concerned about a herpes infection, which is treatable if detected early, which led to Dr. Cheng's urgency in ensuring that A.S. receive treatment. *Id.* at 276. Dr. Wiznitzer also said he believed herpes encephalopathy was unlikely because it would have occurred soon after birth and "is never indolent. It's very dramatic." *Id.* at 277. Based on Dr. Cheng's evaluation, his primary concern seemed focused on A.S.'s failure to thrive and not on an acute encephalopathy. *Id.* at 279.

Regarding Petitioners' statements about A.S. "falling off a cliff," Dr. Wiznitzer believed these are "inaccurate representations of her clinical history." Tr. at 280. A.S. had a history of feeding difficulties that gradually became more obvious; the feeding inefficiency became more apparent as the bigger an infant grows, the more food she requires to continue growing. *Id.* Although Petitioners have a video of A.S. from May 2012, based on the history Petitioners provided to Drs. Douglas and Cheng, vision deterioration occurred soon after and prior to the June 18th vaccinations. *Id.* at 281. Dr. Wiznitzer also reiterated that spasticity occurs over a period of a few weeks. *Id.* There were no fundamental differences between A.S. from when she was observed by Dr. Douglas on June 18, 2012 and when she was seen by Dr. Cheng on June 20, 2012. *Id.*

Dr. Wiznitzer next reviewed the medical records from A.S.'s six day stay at CHOA. Tr. at 284-98. If Petitioners' experts' theory was accurate regarding mitochondrial dysfunction, there

would be evidence of brain cell death, and A.S.'s EEG or MRI would have been abnormal. This was not the case. *Id.* at 284-87. A.S.'s head circumference also had not changed in percentile for the first three years of her life "to any appreciable degree"; thus according to Dr. Wiznitzer, A.S. did not suffer from an acute injury to the brain related to the vaccines. *Id.* at 291. A.S. was recorded as alert and active, not encephalopathic, at the CHOA Emergency Department. *Id.* at 293. When A.S. was seen by Dr. Bruce, the medical records noted that around five months, A.S. had difficulty focusing on Mrs. Svagdis' face.

4. Post-Hearing Reports

Dr. Wiznitzer submitted two post-hearing expert reports. In his first post-hearing report, he responded primarily to Dr. Kinsbourne's conclusions as to why A.S.'s MRI scans were normal. Third Wiznitzer Rep. at 1. Dr. Wiznitzer stated that Dr. Kinsbourne was "incorrect in his differentiation between mitochondrial encephalopathy and anoxic encephalopathy." *Id.* at 2. Dr. Wiznitzer wrote that, while both types of encephalopathy have different triggering mechanisms, "the end result is the same", and they would therefore show the same result on an MRI. *Id.*

Dr. Wiznitzer also noted that A.S.'s MRI scans used newer modalities that are more sensitive and able to identify the brain damage from mitochondrial disorders than routine T1 and T2 imaging. Referencing the MRI report from June 21, 2012, he noted that it "would have identif[ied] the alleged mitochondrial dysfunction if present." *Id.* at 3.

Dr, Wiznitzer also disputed Dr. Kinsbourne's characterization of A.S.'s EEG scans, noting that, regardless of any seizures, if A.S. suffered from a mitochondrial or metabolic encephalopathy, her EEG scans would have been abnormal. *Id.* at 3. As her scans were normal, Dr. Wiznitzer stated that this is "consistent with the conclusion that [A.S.] did not have a mitochondrial or metabolic encephalopathy as the reason for the claimed clinical state change…." *Id.*

In his second post-hearing expert report, Dr. Wiznitzer commented that in his February 12, 2020 expert report, Dr. Kinsbourne "ignore[ed] the objective findings in the records that A.S. had no clinical evidence of encephalopathy as shown on examination and on EEG at the time of her June 20, 2012 hospital admission." Fourth Wiznitzer Rep. at 2. Dr. Wiznitzer also restated his conclusion that "Dr. Kinsbourne's speculation about the presence of a mitochondrial disorder/dysfunction and the role of neuroimaging is not supported by his references or by the medical records." *Id.*

E. Respondent's Expert: Dr. Christine McCusker

1. Qualifications

Dr. McCusker received her medical degree from McMaster University Medical School in 1993 and completed a pediatrics residency at the Montreal Children's Hospital and a clinical fellowship in allergy and immunology at McGill University. Ex. D (hereinafter "McCusker CV") at 1-2. Dr. McCusker is board certified in pediatrics and is a fellow of the Royal College of Physicians and Surgeons of Canada in Pediatrics and Allergy and Immunology. *Id.* at 2. Dr. McCusker is an Associate Member of the Department of Medicine at McGill University and

Research Director at the Meakins-Christie Laboratories and McGill University. *Id.* at 3. Dr. McCusker also serves as the Director of Clinical Immunology Laboratory and Division Director of Pediatric Allergy, Immunology, and Dermatology at Montreal Children's Hospital. *Id.* Dr. McCusker is an ad hoc reviewer for a number of journals including (but not limited to), Journal of Allergy and Clinical Immunology, Journal of Rheumatology, Life Science Journal, Immunobiology, Journal of Medical Genetics, and Pediatric Pulmonology. *Id.* at 14-15. Dr. McCusker has been awarded numerous research grants and has four patents. *See id.* at 21-23. Dr. McCusker has published approximately 75 papers and abstracts. *See id.* at 24-32.

2. Expert Reports

Dr. McCusker first defined cytokines as "small proteins released from cells in response to specific stimuli….which shape the innate and adaptive immune response." First McCusker Rep. at 3-4. She noted that the "purpose of vaccination is to stimulate the development of…adaptive immunity against pathogens in the form of antibodies and specific T cells" and that "the magnitudes of cytokine responses induced by vaccination are much lower than in natural infection…." *Id.* at 4.

Dr. McCusker also discussed recall responses, stating that "upon subsequent exposures to the same pathogen[,] the presence of immunological memory, in the form of antibodies, results in rapid clearance of the pathogen from the system, with only limited activation of the innate, pro-inflammatory pathways." *Id.* at 4. Dr. McCusker stated that "recall…responses to pathogens result in greater specificity and more rapid adaptive responses to these pathogens, leading to rapid clearance without significant or prolonged activity of the pro-inflammatory immune response." *Id.* Dr. McCusker stated that there are "no reports of fever or evidence of inflammation at the site of vaccine" in children receiving their third set of vaccines, as in A.S.'s case. *Id.* at 4-5.

Dr. McCusker then discussed cytokines and vaccination, stating that in comparison to natural infection, vaccination results in a markedly reduced activation of innate pathways. *Id.* at 5. Vaccination is "predicted to activate immune responses in part through cytokine upregulation." *Id.* Citing the Kashiwagi article, Dr. McCusker noted that development of fever was independent of the levels of the cytokines in a child's blood, and that the data suggested that "cytokines are produced and released by the peripheral immune system during vaccination but there is no evidence to suggest that the levels are sufficient to influence…development of cytokine-mediated changes in seizure thresholds…." *Id.* at 5. Citing several studies, Dr. McCusker concluded that "while cytokines are released by vaccination, the levels are extremely low, even in the case of booster vaccination." *Id.* She therefore disagreed with Dr. Kinsbourne that "pro-inflammatory cytokines released following the vaccinations [A.S.] received acted to increase[] oxidative stress in her central nervous system leading to seizures." *Id.* at 6. To support her point, Dr. McCusker noted that A.S. showed no signs of fever, hypoxia, or trauma following her vaccinations, and she was diagnosed with infantile spasms only several months after her vaccinations, at a time "when any vaccination-related cytokine release would have long-since resolved." *Id.*

Finally, Dr. McCusker discussed A.S.'s symptoms in the context of vaccine inducement. Noting that A.S. eventually developed developmental delays and seizures with no defined etiology, Dr. McCusker stated that "there is no clinical evidence that the vaccinations [A.S.] received on 06-

18-2012 induced significant release of proinflammatory cytokines." *Id.* Although there is experimental evidence in mice showing that cytokines can induce seizures, the levels of cytokines required to induce these changes are ">1000X" found post-vaccination. *Id.* at 8. Taken altogether, Dr. McCusker stated that there is no evidence linking vaccinations with developmental delay, even in those children with abnormal neurological development." *Id.*

In her second expert report, Dr. McCusker responded to Dr. Gershwin's assertion that A.S. suffered from a genetic mitochondrial defect, which led to "alterations in cell energy metabolism [which] would influence the target tissue response to cytokines." Second McCusker Rep. at 2. Dr. McCusker summarized Dr. Gershwin's theory to mean that "cytokine production following vaccination in this context resulted in worsening inflammation, altered cellular process and [caused] neurological decline." *Id.* at 2.

Dr. McCusker then conducted a review of the literature Dr. Gershwin cited to support this theory. She stated that "the articles submitted by Dr. Gershwin demonstrate that mitochondrial damage can activate proinflammatory pathways resulting in the release of cytokines.", however, "the articles presented **do not** suggest that in parties with genetic mitochondrial defects, there are any changes in target tissue responses to peripheral cytokine release as hypothesized by Dr. Gershwin." *Id.* at 4 (emphasis in original).

Dr. McCusker concluded her report by restating her conclusion from her first report, that "there is no evidence…of a genetic mitochondrial defect in A.S. despite multiple investigations." *Id.* at 4. She also states that "even were such a defect to be found, the literature submitted by Dr. Gershwin does not support the contention that a child with mitochondrial dysfunction will be more susceptible to cytokine-mediated accelerated neurological decline following vaccination." *Id.*

3. Testimony

I recognized Dr. McCusker as an expert in pediatrics and pediatric immunology and allergy. Tr. at 457. Dr. McCusker testified about the immune system's response post-vaccination. *Id.* at 460-63. She then provided testimony regarding the effects of booster vaccinations. *Id.* at 463-66. Dr. McCusker stated that neither the adaptive nor the innate immune systems start at zero and thus the response becomes more targeted with each subsequent booster. *Id.* at 464. As it relates to A.S., if one has a mitochondrial condition, one is unlikely to generate inflammation as it is an energy-consuming process. *Id.* at 468-69.

Regarding Dr. Gershwin's theory, Dr. McCusker disagreed on a few points. Cytokines do not have a long half-life in the body; IL-1 beta has a half-life of 19 minutes. Tr. at 473. The idea that cytokines, which are diluted in the blood stream, circulated in sufficient amounts to cross the blood-brain barrier and caused an abnormal response in the brain is not a viable theory. *Id.* at 474. A.S. had no fever, no redness at the injection site, or anything indicating that she was experiencing an abnormally high cytokine response. *Id.* Assuming that cytokines did cross the blood-brain barrier, Dr. McCusker noted that they interact differently in the central nervous system; for, instance IL-1 beta is involved with memory formation and the sleep cycle in the CNS. *Id.* at 476-77. Dr. McCusker further noted that the mechanism proposed by Dr. Gershwin has no support in the medical literature. *Id.* at 478. If cytokines did travel to the central nervous system and cause

cell death, Dr. McCusker testified that it would be visible on an MRI or EEG as this would be a cyclical process, where cell death causes more inflammation which causes more cell death. *Id.* at 481-82.

If Dr. Gershwin's mechanism were accurate, when A.S. contracted an upper respiratory tract infection in September 2012, one would expect a similar response as A.S. had physical symptoms and cytokines were activated as an immune response, however A.S. had no neurological changes. Tr. at 483-84. Dr. McCusker ultimately testified that A.S.'s regression would have been the same without the vaccinations. *Id.* at 492.

F. Respondent's Expert: Dr. Shawn McCandless

1. Qualifications

Dr. McCandless received his medical degree from Temple University in 1988 and completed a residency in medical genetics and a fellowship in biochemical genetics. Ex. F (hereinafter "McCandless CV") at 1. Dr. McCandless is an associate professor of Genetics, Pediatrics, and Pathology at Case Western Reserve University and is board certified in pediatrics, clinical genetics, and clinical biochemical genetics. *Id.* Dr. McCandless serves as the Director of the Center for Human Genetics at Case Western Reserve University and University Hospital of Cleveland Case Medical Center; Residency Director of the Case Medical Center, Department of Genetics; Medical Director of the Prader-Willi Syndrome Clinic; and Associate Director of the Center for Inherited Disorders of Energy Metabolism. *Id.* at 2. Dr. McCandless is an ad hoc reviewer for a number of journals (including but not limited to), Genetics in Medicine, Pediatrics, The American Journal of Medical Genetics, Human Molecular Genetics, and more. *Id.* at 2-3. Dr. McCandless has published approximately 50 peer-reviewed papers and abstracts. *Id.* at 5-6, 10-11.

Dr. McCandless now works at the University of Colorado School of Medicine and Children's Hospital Colorado where he is the section head for Genetics and Metabolism in the Department of Pediatrics. Ex. H at 1. During the course of his career, he has treated approximately 100 children and adults with clinically confirmed mitochondrial disorders. Tr. at 329. He has evaluated laboratory testing of 300-500 individuals for mitochondrial disease. *Id.* I recognized Dr. McCandless as an expert in pediatrics, genetics, pediatric metabolic disease (including mitochondrial disorders), and biochemical genetic testing. *Id.* at 331.

2. Expert Reports

Dr. McCandless filed four reports in this case, two of which were filed after the entitlement hearing. Ex. E (hereinafter "First McCandless Rep."), Ex. H (hereinafter "Second McCandless Rep."), Ex. P (hereinafter "Third McCandless Rep."), and Ex. S (hereinafter "Fourth McCandless Rep."). Dr. McCandless also testified at the entitlement hearing.

In his first report, Dr. McCandless summarized A.S.'s current condition as a "child who had subtle, but clear, developmental issues identified from early in life, well before her 6-month immunizations were given on June 18, 2012." First McCandless Rep. at 3. To support this

contention, Dr. McCandless stated that "before she was given the 6-month immunizations, her pediatrician was concerned enough to recommend evaluation by a neurologist and ophthalmologist." *Id.*

Dr. McCandless defined a "primary mitochondrial disorder" as "a constellation of symptoms that have their direct cause due to inadequacy of the mitochondrial energy producing process." First McCandless Rep. at 3. *Citing* Haas; Smeitnik et al., *Mitochondrial medicine: A metabolic perspective on the pathology of oxidative phosphorylation disorders*, 3 CELL METABOLISM, 9-13 (2006) (filed as Ex. K, Tab 5). Dr. McCandless noted that there are a variety of "red-flag" symptoms and laboratory findings that are typically suggestive of mitochondrial disorder. The diagnosis of primary mitochondrial disease therefore requires a combination of "appropriate clinical findings and suggestive laboratory abnormalities." *Id.* Dr. McCandless stated that, "the more specific and persisting the findings are, both clinical and laboratory, the more convincing the argument for primary mitochondrial disease." *Id.*

Based on the records provided, Dr. McCandless concluded that "there is not persuasive evidence" that A.S. suffered from a primary mitochondrial disorder. *Id.*at 5. He reviewed the list of symptoms from the Haas article and concluded that A.S. lacked any clear 'red-flag' symptom of mitochondrial disease. *Id.* at 5. Dr. McCandless did not see "evidence in the record of an acute encephalopathy or severe dysmotility that would be strongly suggestive of a primary mitochondrial disorder." *Id.* He did not see suggestive biochemical markers of mitochondrial dysfunction in any of A.S.'s tests. *Id.*

Dr. McCandless then disagreed with Dr. Boles' assertion that A.S. suffered from elevations in her lactic acid. *Id.* at 5. Dr. McCandless stated that the values found were "trivially above the upper end of the reference interval" and in his experience, were "related to difficulty with obtaining free flowing blood samples from children and use of a torniquet" rather than to a mitochondrial disease. *Id.* In his lab, Dr. McCandless uses a "cut-off" value of >150% of the upper reference interval to avoid "over or inappropriate diagnosis of primary mitochondrial disease." *Id.* He also disagreed with Dr. Boles that a physician independently diagnosed significant developmental regression in A.S., stating that "any reference to an association between regression and vaccination in the records was based on the parent's report, well after the events transpired." *Id.* Furthermore, he disagreed with Dr. Boles that A.S. "fell off a cliff" stating "there was not documentation of an acute loss of all milestones", stating that based on the records, it was clear that A.S. "was not a normal 6-month old." *Id.* Dr. McCandless also disagreed with Dr. Boles that "gastrointestinal dysmotility at different levels is common in patients with mitochondrial dysfunction/disorders" *Id.* at 7.

Dr. McCandless also refuted the assertion that the molecular test results were supportive of primary mitochondrial disease. First McCandless Rep. at 5. He stated that the NDUFA1 variant identified is present in A.S.'s father, who does not suffer from mitochondrial disease. The gene is on the X chromosome and "it is a generally accepted principal of clinical genetics that an X chromosome variant that does not cause disease in a male is not a reasonable explanation for disease in a female." *Id.* Dr. McCandless also downplayed the importance of the buccal swab analysis stating that the test is "still in a research state…and has not yet been completely established nor replicated." *Id.* at 6. He stated that the test "should not be considered clinically

diagnostic [and that] is strongly emphasized by both the performing scientist and the interpreting physician in the report." *Id.*

Dr. McCandless concluded his report by stating that A.S. "had neurodevelopmental abnormalities apparent in the first few months of life, she does not have sufficient findings to confirm a diagnosis of primary mitochondrial disease", and that he found "no compelling evidence that the vaccines she received contributed to her severe neurological disorder." *Id.* at 10.

In Dr. McCandless' second expert report, he rebutted Dr. Gershwin's assertion that A.S. suffered from a genetic mitochondrial defect which led to alterations in cell energy metabolism, which in turn influenced the target tissue response to cytokines. Second McCandless Rep. at 2. Dr. McCandless understood Dr. Gershwin's theory to be that "cytokine production following vaccination in … resulted in worsening inflammation, altered cellular process and neurological decline." *Id.* Dr. McCandless conducted a review of the literature submitted by Dr. Gershwin to support this point. He concluded that none of the literature submitted suggested that in patients with genetic mitochondrial defects, there are changes in target tissue responses to peripheral cytokine release. He noted that much of the literature focuses on the role of mitochondrial products in the activation and release of cytokines not in response to peripheral cytokines such as those present systemically, "albeit in minimal amounts" following vaccination. *Id.* at 4.

Dr. McCandless concluded his expert report by stating that the records provide no evidence that A.S. suffers from a genetic mitochondrial defect, and, even if she did, the literature Dr. Gershwin provided "does not support the contention that a child with mitochondrial dysfunction will be more susceptible to cytokine-mediated accelerated neurological decline following vaccination." Second McCandless Rep. at 5.

3. Testimony

I recognized Dr. McCandless as an expert in pediatrics, genetics, and pediatric metabolic disease, including mitochondrial disorders, and biochemical genetic testing. Tr. at 331. Dr. McCandless testified that he did not believe that "compelling or convincing evidence" existed to demonstrate that A.S. suffered from a mitochondrial dysfunction, and "there's certainly not a diagnosis of mitochondrial disease." Tr. at 332.

Dr. McCandless explained the difference between mitochondrial dysfunction and mitochondrial disease is that mitochondrial disease is "generally accepted to be a constellation of signs and symptoms that are caused by a defect in one component of mitochondrial energy metabolism," Tr. at 333. He clarified this to mean that "when we talk about mitochondrial disease or primary mitochondrial diseases, that means a defect in one component of the electron transport chain or multiple components of the electron transport chain that…is the primary cause of the signs and symptoms that the patient is dealing with." *Id.*

Mitochondrial dysfunction, on the other hand, is used to "reflect abnormalities in laboratory testing that suggest that the mitochondrial electron transport chain is not functioning normally. It is agnostic to the cause of that dysfunction." Tr. at 333. He clarified this to mean that mitochondrial dysfunction "refers to laboratory findings that are suggestive of an alteration in the

function of that electron transport chain in the mitochondria." *Id.* at 334. Dr. McCandless explained that "if you can find a genetic change or clinical findings that are completely consistent with the laboratory findings in someone that has laboratory evidence of mitochondria dysfunction, you can make a diagnosis of primary mitochondrial disease." *Id.* at 333. The fundamental question to differentiate the two is if someone is discussing "dysfunction in any enzyme found in the mitochondria," they mean mitochondrial dysfunction, but if they specifically mean "dysfunction of the electron transport chain", they are talking about mitochondrial disease. *Id.* at 333-34.

Dr. McCandless next discussed the question as to whether A.S. "fell off a cliff" as far as her status following vaccinations. Tr. at 335. He disagreed with this point stating that "there are a number of entries in the contemporaneous medical records that indicate that there was a gradually evolving picture of neurologic dysfunction in A.S." *Id.* Dr. McCandless stated that the "concept that there was an acute change…is primarily based on the history as the parents described it to various providers." *Id.* As evidence, Dr. McCandless pointed to the fact that A.S. was eating very little for a child her age at her four-month visit. *Id.* at 337. Furthermore, at her six-month visit, she was eating even less than she was at the four-month visit. *Id.* Finally, Dr. McCandless pointed to the fact that A.S. rolled at two months as evidence of likely neurological dysfunction because at that age, "if there's an abnormality or an asymmetry of the tone in the arms or spasticity in the arms…when a child tries to push up, he may have one arm that pushes more than the other, and the baby just kind of flips over from stomach to back." *Id.* at 340. Dr. McCandless couched this opinion by saying he would defer to the neurologist about how specific or sensitive that particular finding is." *Id.* at 341.

Based on A.S.'s reduced caloric intake, Dr. McCandless opined it was extremely unlikely she was suffering from a mitochondrial dysfunction. Tr. at 337. Dr. McCandless noted that because A.S. continued to gain weight, this meant that her mitochondria were "working very efficiently to extract every bit of energy she can from the food she's taking in." *Id.* at 339.

Following this, Dr. McCandless testified that he disagreed with Dr. Boles opinion that A.S., "more likely than not, had a mitochondrial dysfunction." *Id.* at 341. He agreed with Dr. Boles that there are no "gold standard" tests that can definitively show mitochondrial dysfunction. *Id.* at 342. He testified that there are several different types of tests that try to show mitochondrial dysfunction, but "molecular testing…is the closest we have to a gold standard." *Id.* at 343. If "you find a genetic change that is consistent, that's been seen many times before in mitochondrial disease, you can be confident that that's the diagnosis…." *Id.*

Turning his focus to A.S.'s lab reports, Dr. McCandless noted that, although Dr. Boles stated that A.S.'s plasma lactate was "mildly elevated," there are very few mitochondrial experts in the world who would consider those significantly elevated lactate values." Tr. at 345. Patients with a diagnosis of mitochondrial disease had lactate levels "at least 150 percent of the upper limit of normal of the range." *Id.* at 347. Dr. McCandless indicated that none of A.S.'s molecular testing showed mitochondrial dysfunction, much less mitochondrial disease. *Id.* at 346-47. Dr. McCandless also testified that A.S.'s testing for urine organic acids was not "specific or even highly suggestive of mitochondrial dysfunction. *Id.* at 350. He noted that the two markers that were important in this testing were 3-methylglutaric acid, and 3-methylglutaconic acid, and neither one was elevated in A.S.'s sample. *Id.* at 352. He further stated that "the things Dr. Boles pointed

to in his sample as indicative of mitochondrial disease are not indicative of mitochondrial disease…they are normal variants." *Id.*

Dr. McCandless also took issue with Dr. Boles' assertion that the pattern of the plasma acylcarnitines in A.S. was highly suggestive of mitochondrial disorder. Tr. at 352-53. Dr. McCandless noted that firstly, acylcarnitine analysis "is not generally thought to be highly informative for mitochondrial disorders." *Id.* at 353. Secondly, even if it were, the pattern seen in A.S. is not the typical pattern seen in patients with mitochondrial disorders. *Id.* Rather, this is the pattern seen in patients who are taking supplemental carnitine, which A.S. was. *Id.* at 353-54. Dr. McCandless testified that as a result of the supplemental carnitine, A.S. had extra carnitine in the mitochondria. *Id.* at 354. Dr. McCandless noted that if Dr. Boles only measured acylcarnitines in patients on carnitine, he would see this pattern in all patients he believed to have mitochondrial disease. *Id.* at 355. In relation to A.S.'s case, Dr. McCandless noted that on June 22, 2012, when A.S. was allegedly at her sickest, her "acetyl, C3, C4OH, they are all completely normal. So if those are indicative of mitochondrial dysfunction, why would they not be elevated when this child is supposedly the sickest she has ever been because of mitochondrial dysfunction?" *Id.* at 357.

Dr. McCandless next commented on the electron transport chain analysis performed from a buccal swab which allegedly revealed "mitochondrial proliferation and complex IV deficiency." Tr. at 358. Dr. McCandless first stated that this "is not a test that is widely accepted by mitochondrial experts as having significant value." *Id.* at 389-59. The test is "relatively new" and the single publication in the literature describing the test "doesn't provide the validation data that laboratory would need for proposing a diagnostic test." *Id.* at 359. In particular, Dr. McCandless stated that the test lacks sensitivity and specificity. *Id.* He stated that the test lacks sensitivity because "in the paper they suggest it's about 70 or 80 percent sensitive…so it may contribute some information but it's certainly not a diagnostic test" and it lacks specificity because the positive predictive value (what percentage of positive tests are false positives) is not known for this test." *Id.* at 360. Ultimately, Dr. McCandless testified that the samples are not reliable because too much about the validity of the test is unknown. *Id.*

Dr. McCandless then testified that he disagreed with Dr. Gershwin's assertion that "there's something special about [A.S.'s] mitochondrial DNA…[and] people that already have decreased mitochondrial function are going to be at higher risk from…cytokines." Tr. at 366. Dr. McCandless stated that A.S.'s entire mitochondrial DNA has been sequenced and found to be normal, except "two variants that are not known to be completely normal, except that they both occur…in some number of normal people in the population." *Id.*

Finally, Dr. McCandless stated that he found "no compelling clinical findings that pointed to mitochondrial disease." Tr. at 371. The only test that possibly pointed to mitochondrial disease is the buccal swab, and in Dr. McCandless opinion, this test is not "a particularly good test." *Id.* Dr. McCandless also highlighted two additional pieces of evidence regarding the absence of mitochondrial disease. First, none of her medical records refer to mitochondrial disease over the last two years, and she is not on treatment for it. Secondly, a neurologist placed her on valproic acid, which, if given to a patient with mitochondrial disease, would cause liver failure. *Id.* at 372-73.

4. Post-Hearing Reports

In his third expert report, Dr. McCandless refuted Dr. Kinsbourne's explanation as to why A.S.'s MRI scans did not show evidence of injury typically seen in mitochondrial disease. Third McCandless Rep. at 1. Dr. McCandless characterized Dr. Kinsbourne's theory as saying that if A.S. had primary mitochondrial dysfunction, Dr. Kinsbourne would expect to see different injuries on an MRI than those expected with anoxia/hypoxia. *Id.*

Dr. Kinsbourne opined that A.S. "fell off a cliff" following her June 18, 2012, vaccines. *Id.* Dr. McCandless pointed out that "if that were the case, that there was an acute and severe failure of mitochondrial function, one would reasonably expect to see MRI changes." *Id.* He went on to say that while "their absence does not rule out mitochondrial disease, [] it certainly undermines the "falling off the cliff" argument." *Id.*

Dr. McCandless also addressed Dr. Kinsbourne's claim that "the absence of MRI changes in the presence of objective major clinical/behavioral regression is further evidence for a metabolic cause, such as a mitochondrial insufficiency." First McCandless Rep. at 1. To rebut this argument, Dr. McCandless pointed out that mitochondrial diseases associated with regression typically are associated with MRI changes, and the absence of evidence of injury on an MRI scan undercuts the argument that A.S. suffers from a mitochondrial disease. *Id.* at 1-2.

In his fourth expert report, Dr. McCandless restated his conclusion that A.S. did not suffer from mitochondrial disease, but that "the most likely explanation for [A.S.]'s neurodevelopmental disorder is that there is a genetic variant that we currently don't have the ability to recognize that explains her altered brain development." Fourth McCandless Rep. at 2. He also reiterated that an MRI scan can contribute information regarding a potential mitochondrial disorder, but it's simply one of many possible sources. *Id.* at 1-2.

V. Applicable Law

A. Petitioner's Burden in Vaccine Program Cases

Under the Vaccine Act, when a petitioner suffers an alleged injury that is not listed in the Vaccine Injury Table, a petitioner may demonstrate that he suffered an "off-Table" injury. § 11(c)(1)(C)(ii).

In attempting to establish entitlement to a Vaccine Program award of compensation for a off-Table claim, a petitioner must satisfy all three of the elements established by the Federal Circuit in *Althen v. Sec'y of Health & Hum. Servs.*, 418 F.3d 1274 (Fed. Cir. 2005). *Althen* requires that petitioner establish by preponderant evidence that the vaccination he received caused his injury "by providing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *Id.* at 1278.

Under the first prong of *Althen*, petitioners must provide a "reputable medical theory," demonstrating that the vaccine received *can cause* the type of injury alleged. *Pafford*, 451 F.3d at

1355-56 (citations omitted). To satisfy this prong, a petitioner's theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen v. Sec'y of Health & Hum. Servs*., 35 F.3d 543, 548 (Fed. Cir. 1994). Proof that the proffered medical theory is reasonable, plausible, or possible does not satisfy a petitioner's burden. *Boatmon v. Sec'y of Health & Hum. Servs*., 941 F.3d 1351, 1359-60 (Fed. Cir. Nov. 7, 2019).

Petitioners may satisfy the first *Althen* prong without resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory. *Andreu v. Sec'y of Health & Hum. Servs.*, 569 F.3d 1367, 1378-79 (Fed. Cir. 2009) (citing *Capizzano*, 440 F.3d at 1325-26). However, special masters are "entitled to require some indicia of reliability to support the assertion of the expert witness." *Boatmon*, 941 F.3d at 1360, *quoting Moberly*, 592 F.3d at 1324. Special Masters, despite their expertise, are not empowered by statute to conclusively resolve what are complex scientific and medical questions, and thus scientific evidence offered to establish *Althen* prong one is viewed "not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Id.* at 1380. Accordingly, special masters must take care not to increase the burden placed on petitioners in offering a scientific theory linking vaccine to injury. *Contreras v. Sec'y of Health & Hum. Servs*., 121 Fed. Cl. 230, 245 (2015), *vacated on other grounds*, 844 F.3d 1363 (Fed. Cir. 2017); *see also Hock v. Sec'y of Health & Hum. Servs*., No. 17-168V, 2020 U.S. Claims LEXIS 2202 at *52 (Fed. Cl. Spec. Mstr. Sept. 30, 2020).

The second *Althen* prong requires proof of a logical sequence of cause and effect, usually supported by facts derived from a petitioner's medical records. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375-77; *Capizzano*, 440 F.3d at 1326 ("medical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause-and-effect show[s] that the vaccination was the reason for the injury'") (quoting *Althen*, 418 F.3d at 1280). Medical records are generally viewed as particularly trustworthy evidence, since they are created contemporaneously with the treatment of the patient. *Cucuras v. Sec'y of Health & Hum. Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993).

However, medical records and/or statements of a treating physician's views do not *per se* bind the special master to adopt the conclusions of such an individual, even if they must be considered and carefully evaluated. Section 13(b)(1) (providing that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court"). As with expert testimony offered to establish a theory of causation, the opinions or diagnoses of treating physicians are only as trustworthy as the reasonableness of their suppositions or bases. The views of treating physicians should also be weighed against other, contrary evidence also present in the record. *Hibbard v. Sec'y of Health & Hum. Servs*., 100 Fed. Cl. 742, 749 (2011), *aff'd*, 698 F.3d 1355 (Fed. Cir. 2012); *Caves v. Sec'y of Health & Hum. Servs*., No. 06-522V, 2011 WL 1935813, at *17 (Fed. Cl. Spec. Mstr. Apr. 29, 2011), *mot. for review den'd*, 100 Fed. Cl. 344, 356 (2011), *aff'd without opinion*, 475 Fed. App'x 765 (Fed. Cir. 2012).

The third *Althen* prong requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. That term has been equated to the phrase "medically-acceptable temporal relationship." *Id.* A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical

understanding of the disorder's etiology, it is medically acceptable to infer causation." *de Bazan v. Sec'y of Health & Hum. Servs*., 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one's requirement). *Id.* at 1352; *Shapiro v. Sec'y of Health & Hum. Servs*., 101 Fed. Cl. 532, 542 (2011), *recons. den'd after remand*, 105 Fed. Cl. 353 (2012), *aff'd mem*., 503 F. App'x 952 (Fed. Cir. 2013); *Koehn v. Sec'y of Health & Hum. Servs*., No. 11-355V, 2013 WL 3214877 (Fed. Cl. Spec. Mstr. May 30, 2013), *mot. for review den'd* (Fed. Cl. Dec. 3, 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014).

In the present case, Petitioners allege that A.S. suffered an off-table significant aggravation of her pre-existing neurological condition as a result of receiving the DTaP, IPV, Hib, Hep. B, Prevnar and/or RotaTeq vaccinations on June 18, 2012. Amended Pet. at 2.

The Vaccine Act defines significant aggravation as "any change for the worse in a preexisting condition which results in markedly greater disability, pain, or illness accompanied by substantial deterioration of health." § 300aa-33(4). In *Loving*, the United States Court of Federal Claims established the governing six-part test for off-Table significant aggravations. Petitioner must prove by a preponderance of the evidence:

> (1) The person's condition prior to administration of the vaccine, (2) the person's current condition (or the condition following the vaccination if that is also pertinent), (3) whether the person's current condition constitutes a 'significant aggravation' of the person's condition prior to vaccination, (4) a medical theory causally connecting such a significant worsened condition to the vaccination, (5) a logical sequence of cause and effect showing that the vaccination was the reason for the significant aggravation, and (6) a showing of a proximate temporal relationship between the vaccination and the significant aggravation.

Loving v. Sec'y of Health & Hum. Servs., 86 Fed. Cl. 135, 144 (2009); *see also W.C. v. Sec'y of Health & Human Servs.*, 704 F.3d 1352, 1357 (Fed. Cir. 2013) (adopting this as the proper legal standard for significant aggravation claims brought under the Vaccine Act). *Loving* prongs four, five, and six are derived from the Federal Circuit's test for off-Table actual causation cases. *Althen v. Sec'y of Health & Hum. Servs.*, 17 F.3d 374 (Fed. Cir. 1994).

In *Sharpe*, the Federal Circuit clarified the *Loving* prongs and what is required by petitioners to successfully demonstrate a causation-in-fact significant aggravation claim. *Sharpe v. Sec'y of Health & Hum. Servs.,* 964 F.3d 1072 (Fed. Cir. 2020). *Loving* prong three only requires a comparison of a petitioner's current, post-vaccination condition with her pre-existing pre-vaccination condition. *Sharpe* at 1082; *Whitecotton v. Sec'y of Health & Hum. Servs.,* 81 F.3d 1099 (Fed. Cir. 1996). A petitioner is not required to demonstrate an expected outcome or that her post-vaccination condition was worse than such an expected outcome. *Sharpe* at 1081.

Under *Loving* prong four, a petitioner need only provide a "medical theory causally connecting [petitioner's] significantly worsened condition to the vaccination." *Sharpe* at 1083; *see also Loving*, 86 Fed. Cl. at 144. In other words, petitioner is required to present a medically reliable theory demonstrating that a vaccine "can cause a significant worsening" of the condition. *Sharpe*

at 1083 (citing to *Pafford ex. rel. Pafford v. Sec'y of Health & Hum. Servs.*, 451 F.3d 1352, 1356-57 (Fed. Cir. 2006). A petitioner may be able to establish a prima facie case under *Loving* prong four without eliminating a pre-existing condition as the cause of her significantly aggravated injury. *Id.*; citing *Walther v. Sec'y of Health & Hum. Servs.,* 485 F. 3d 1146, 1151 (Fed. Cir. 2007) (noting that "the government bears the burden of establishing alterative causation. . . . once petitioner has established a prima facie case").

Loving prong five requires a petitioner to show "a logical sequence of cause and effect showing that the vaccination was the reason for the significant aggravation." *Loving,* 86 Fed. Cl. at 144. In other words, petitioner must show that the vaccinations "did" cause a worsening of [petitioner's underlying disorder]. *Id.*

In determining whether a petitioner is entitled to compensation, a special master must consider the entire record and is not bound by any particular piece of evidence. § 13(b)(1) (stating that a special master is not bound by any "diagnosis, conclusion, judgment, test result, report, or summary" contained in the record). Furthermore, a petitioner is not required to present medical literature or epidemiological evidence to establish any *Althen* prong. The special master essentially must weigh and evaluate opposing evidence in deciding whether a petitioner has met their burden of proof. *Andreu v. Sec'y of Health & Hum. Servs.*, 569 F.3d 1367, 1380 (Fed. Cir. 2009); *see also Grant v. Sec'y of Health & Hum. Servs.*, 956 F.2d 1144, 1149 (Fed. Cir. 1992).

B. Law Governing Analysis of Fact Evidence

The process for making factual determinations in Vaccine Program cases begins with analyzing the medical records, which are required to be filed with the petition. Section 11(c)(2). The special master is required to consider "all [] relevant medical and scientific evidence contained in the record," including "any diagnosis, conclusion, medical judgment, or autopsy or coroner's report which is contained in the record regarding the nature, causation, and aggravation of the petitioner's illness, disability, injury, condition, or death," as well as the "results of any diagnostic or evaluative test which are contained in the record and the summaries and conclusions." Section 13(b)(1)(A). The special master is then required to weigh the evidence presented, including contemporaneous medical records and testimony. *See Burns v. Sec'y of Health & Hum. Servs.*, 3 F.3d 413, 417 (Fed. Cir. 1993) (it is within the special master's discretion to determine whether to afford greater weight to contemporaneous medical records than to other evidence, such as oral testimony surrounding the events in question that was given at a later date, provided that such determination is evidenced by a rational determination).

Medical records created contemporaneously with the events they describe are generally trustworthy because they "contain information supplied to or by health professionals to facilitate diagnosis and treatment of medical conditions," where "accuracy has an extra premium." *Kirby v. Sec'y of Health & Hum. Servs.*, 997 F.3d 1378 (Fed. Cir. 2021) citing *Cucuras,* 993 F.2d at 1528. This presumption is based on the linked proposition that (i) sick people visit medical professionals; (ii) sick people honestly report their health problems to those professionals; and (iii) medical professionals record what they are told or observe when examining their patients in as accurate a manner as possible, so that they are aware of enough relevant facts to make appropriate treatment decisions. *Sanchez v. Sec'y of Health & Hum. Servs.*, No. 11-685V, 2013 WL 1880825 at *2 (Fed.

Cl. Spec. Mstr. Apr. 10, 2013) *mot. for rev. denied*, 142 Fed. Cl. 247, 251-52 (2019), *vacated on other grounds and remanded*, 809 Fed. Appx. 843 (Fed. Cir. Apr. 7, 2020).

Accordingly, if the medical records are clear, consistent, and complete, then they should be afforded substantial weight. *Lowrie v. Sec'y of Health & Hum. Servs.*, No. 03-1585V, 2005 WL 6117475 at *20 (Fed. Cl. Spec. Mstr. Dec. 12, 2005). Indeed, contemporaneous medical records are generally found to be deserving of greater evidentiary weight than oral testimony -- especially where such testimony conflicts with the record evidence. *Cucuras*, 993 F.2d at 1528; see also *Murphy v. Sec'y of Health & Hum. Servs.*, 23 Cl. Ct. 726, 733 (1991), *aff'd per curiam*, 968 F.2d 1226 (Fed. Cir. 1992), *cert. den'd*, *Murphy v. Sullivan*, 506 U.S. 974 (1992) (citing *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 396 (1947) ("[i]t has generally been held that oral testimony which is in conflict with contemporaneous documents is entitled to little evidentiary weight.")).

However, there are situations in which compelling oral testimony may be more persuasive than written records, such as where records are deemed to be incomplete or inaccurate. *Campbell v. Sec'y of Health & Hum. Servs.*, 69 Fed. Cl. 775, 779 (2006) ("like any norm based upon common sense and experience, this rule should not be treated as an absolute and must yield where the factual predicates for its application are weak or lacking"); *Lowrie*, 2005 WL 6117475 at *19 ("[w]ritten records which are, themselves, inconsistent, should be accorded less deference than those which are internally consistent") (quoting *Murphy*, 23 Cl. Ct. at 733)). Ultimately, a determination regarding a witness's credibility is needed when determining the weight that such testimony should be afforded. *Andreu*, 569 F.3d at 1379; *Bradley v. Sec'y of Health & Hum. Servs.*, 991 F.2d 1570, 1575 (Fed. Cir. 1993).

When witness testimony is offered to overcome the presumption of accuracy afforded to contemporaneous medical records, such testimony must be "consistent, clear, cogent and compelling." *Sanchez*, 2013 WL 1880825 at *3 (citing *Blutstein v. Sec'y of Health & Hum. Servs.*, No. 90-2808V, 1998 WL 408611 at *5 (Fed. Cl. Spec. Mstr. June 30, 1998)). In determining the accuracy and completeness of medical records, the Court of Federal Claims has listed four possible explanations for inconsistencies between contemporaneously created medical records and later testimony: (1) a person's failure to recount to the medical professional everything that happened during the relevant time period; (2) the medical professional's failure to document everything reported to her or him; (3) a person's faulty recollection of the events when presenting testimony; or (4) a person's purposeful recounting of symptoms that did not exist. *LaLonde v. Sec'y of Health & Hum. Servs.*, 110 Fed. Cl. 184, 203-04 (2013), *aff'd*, 746 F.3d 1334 (Fed. Cir. 2014). In making a determination regarding whether to afford greater weight to contemporaneous medical records or other evidence, such as testimony at hearing, there must be evidence that this decision was the result of a rational determination. *Burns*, 3 F.3d at 417.

C. Analysis of Expert Testimony

Establishing a sound and reliable medical theory connecting the vaccine to the injury often requires petitioners to present expert testimony in support of their claim. *Lampe v. Sec'y of Health & Hum. Servs.*, 219 F.3d 1357, 1361 (Fed. Cir. 2000). Vaccine Program expert testimony is usually evaluated according to the factors for analyzing scientific reliability set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 594-96 (1993). *See Cedillo v. Sec'y of Health & Hum. Servs.*,

617 F.3d 1328, 1339 (Fed. Cir. 2010) (*citing Terran v. Sec'y of Health & Hum. Servs.*, 195 F.3d 1302, 1316 (Fed. Cir. 1999). "The *Daubert* factors for analyzing the reliability of testimony are: (1) whether a theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and (4) whether the theory or technique enjoys general acceptance within a relevant scientific community." *Terran,* 195 F.3d at 1316 n.2 (citing *Daubert,* 509 U.S. at 592-95).

The *Daubert* factors play a slightly different role in Vaccine Program cases than they do when applied in other federal judicial fora. *Daubert* factors are employed by judges to exclude evidence that is unreliable and potentially confusing to a jury. In Vaccine Program cases, these factors are used in the weighing of the reliability of scientific evidence. *Davis v. Sec'y of Health & Hum. Servs.*, 94 Fed. Cl. 53, 66-67 (2010) ("uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted").

Respondent frequently offers one or more experts of his own in order to rebut petitioners' case. Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Hum. Servs.*, 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe*, 219 F.3d at 1362). However, nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder,* 88 Fed. Cl. at 743 (quoting *Gen. Elec. Co. v. Joiner,* 522 U.S. 136, 146 (1997)). A "special master is entitled to require some indicia of reliability to support the assertion of the expert witness." *Moberly,* 592 F.3d at 1324. Weighing the relative persuasiveness of competing expert testimony, based on a particular expert's credibility, is part of the overall reliability analysis to which special masters must subject expert testimony in Vaccine Program cases. *Id.* at 1325-26 ("[a]ssessments as to the reliability of expert testimony often turn on credibility determinations").

D. Consideration of Medical Literature

Although this decision discusses some but not all of the medical literature in detail, I reviewed and considered all of the medical records and literature submitted in this matter. *See Moriarty v. Sec'y of Health & Hum. Servs.*, 844 F.3d 1322, 1328 (Fed. Cir. 2016) ("We generally presume that a special master considered the relevant record evidence even though [s]he does not explicitly reference such evidence in h[er] decision."); *Simanski v. Sec'y of Health & Hum. Servs.*, 115 Fed. Cl. 407, 436 (2014) ("[A] Special Master is 'not required to discuss every piece of evidence or testimony in her decision.'" (citation omitted)), *aff'd*, 601 F. App'x 982 (Fed. Cir. 2015).

VI. Analysis

Petitioners summarized their theory of the case as follows: "[A.S.] faced an increased sensitivity to vaccination-related neurologic disease in June 2012 because of her mitochondrial dysfunction." Pet'r's Post Hearing Brief at 8. "Her innate immune response produced a cytokine

[response] significant enough to create overwhelming oxidative stress due to mitochondrial dysfunction, with the stress causing cell injury leading to a rapid, "precipitous" deterioration." *Id.* at 9. "The vaccines interacted with her dysfunctional mitochondria and accelerated any preexisting or ongoing process in [A.S.]." *Id.* at 10. I will first discuss whether A.S. suffers from mitochondrial dysfunction, and will then turn to an analysis of each of the *Loving* prongs.

A. Petitioner has not Presented Preponderant Evidence that A.S. Suffers from Mitochondrial Dysfunction

Dr. McCandless defined primary mitochondrial disorder as "a constellation of symptoms that have their direct cause due to inadequacy of the mitochondrial energy producing process." First McCandless Rep. at 4; Tr. at 333. In primary mitochondrial disease, the mitochondria do not function normally in a clinically measurable way. *Id.*; *see also Holt v. Sec'y Health & Hum. Servs.*, No. 05–0136V, 2015 WL 4381588, at *23 (Fed. Cl. Spec. Mstr. June 24, 2015) (discussing the distinction between mitochondrial disease and mitochondrial dysfunction).

Mitochondrial dysfunction, on the other hand, is a term used to describe "abnormalities in laboratory testing that suggest that the mitochondrial electron transport chain is not functioning normally." Tr. at 333. As Dr. Boles described, "the mitochondria are not working right." *Id.* at 92. Importantly, this abnormal function is "agnostic [as] to … cause." *Id.* at 333. Thus, in secondary mitochondrial dysfunction, the cause of this improper functioning rests outside of the mitochondria. *Id.* at 93. "[M]itochondrial disease is a subset of mitochondrial dysfunction." *Id.* at 125-26.

By way of example, Dr. Boles explained that type 2 diabetes is, in large part, due to mitochondrial dysfunction. Tr. at 99. However, that does not mean that people with type II diabetes have mitochondrial disease. *Id.* at 98-99.

Dr. Boles opined that A.S. suffers from mitochondrial dysfunction. He testified that his confidence regarding this opinion is "in the 90 percent range." Tr. at 124-25. With respect to mitochondrial disease, Dr. Boles opined that "I am not saying that [A.S.] is more than 50 percent or 90 percent likely to have mitochondrial disease. I don't know. [A.S.] may or may not have mitochondrial disease. My best guess would be 50/50." *Id.* at 126.

Haas describes mitochondrial disease as "not a single entity but, rather, a heterogeneous group of disorders characterized by impaired energy production due to genetically based oxidative phosphorylation dysfunction." Hass's purpose was to facilitate the clinical recognition of mitochondrial disease. Haas at 1326.

Haas listed several "red-flag" symptoms for primary mitochondrial disease.

TABLE 1 Red-Flag Findings in Mitochondrial Disease

Neurologic
Cerebral stroke-like lesions in a nonvascular pattern
Basal ganglia disease
Encephalopathy: recurrent or with low/moderate dosing of valproate
Neurodegeneration
Epilepsia partialis continua
Myoclonus
Ataxia
MRI findings consistent with Leigh disease
Characteristic MRS peaks
Lactate peak at 1.3 ppm TE (time to echo) at 35 and 135
Succinate peak at 2.4 ppm
Cardiovascular
Hypertrophic cardiomyopathy with rhythm disturbance
Unexplained heart block in a child
Cardiomyopathy with lactic acidosis (>5 mM)
Dilated cardiomyopathy with muscle weakness
Wolff-Parkinson-White arrhythmia
Ophthalmologic
Retinal degeneration with signs of night blindness, color-vision deficits, decreased visual acuity, or pigmentary retinopathy
Ophthalmoplegia/paresis
Fluctuating, dysconjugate eye movements
Ptosis
Sudden- or insidious-onset optic neuropathy/atrophy
Gastroenterologic
Unexplained or valproate-induced liver failure
Severe dysmotility
Pseudo-obstructive episodes
Other
A newborn, infant, or young child with unexplained hypotonia, weakness, failure to thrive, and a metabolic acidosis (particularly lactic acidosis)
Exercise intolerance that is not in proportion to weakness
Hypersensitivity to general anesthesia
Episodes of acute rhabdomyolysis

Haas at 1327, Table 1. According to Haas, "[t]hese red flag features warrant the initiation of a baseline diagnostic evaluation for mitochondrial disease." Haas at 1327. According to Dr. Boles, A.S. displayed several of these red flags, to include a recurrent encephalopathy, neurodegeneration, and severe gastrointestinal dysmotility. Tr. at 123.

With respect to a recurrent encephalopathy, Dr. Boles testified that "[e]ncephalopathy just means that the brain is not working right. This patient certainly, in my mind, has encephalopathy." Tr. at 123. Dr. McCandless noted that physicians who want to confirm a diagnosis of primary mitochondrial disorder will interpret some of Haas's red flags more broadly. By way of example, he noted that "'encephalopathy' is a broad term that can include many variations of altered levels of consciousness or brain dysfunction, or it can be applied quite specifically to individuals with an acute, or sub-acute, marked alteration in level of consciousness that is unexplained by other causes, such as seizures." First McCandless Rep. at 4-5. Given the broad definition of the term, A.S., by virtue of experiencing seizures, suffered from recurrent encephalopathy. However, such a broad application does little to advance Petitioners' position that A.S. suffers from mitochondrial dysfunction.

With respect to whether A.S. had neurodegeneration, Dr. Boles testified that "There is neurodegeneration. Again, this patient has neurodegeneration." *Id.* He did not provide any

additional information. Degeneration is defined as "deterioration; change from a higher to a lower form; especially change of tissue to a less functionally active form."[8] Again, given the broad nature of this definition, I agree with Dr. Boles that A.S. had neurodegeneration.

Finally, concerning severe gastrointestinal dysmotility, Dr. Boles opined that the fact that A.S. needed a feeding tube and also at times experienced obstipation suggests that she had severe gastrointestinal dysmotility. Tr. at 123-24. Dr. Boles testified that "[o]bstipation means that the bowels are not just moving slowly, but basically they're not moving at all, they're plugged up. That's a serious medical problem and a red flag for mitochondrial dysfunction." Tr. at 103. A.S. did suffer from periodic obstipation and did require the placement of a feeding tube, however, it is not clear that this constitutes severe gastrointestinal dysmotility. Dr. Wiznitzer testified that obstipation is "very common in my patients like A.S. who basically don't move, who are not as active as they should be. You need to maintain … normal, regular activity in order to actually have good bowel function." Tr. at 298. Dr. McCandless agreed, noting that "Chronic constipation with leakage of watery stool is extremely common in individuals with severe brain abnormalities of any cause." First McCandless Rep. at 8. Accordingly, even assuming that A.S. did experience severe gastric dysmotility, this does not suggest mitochondrial dysfunction.

With respect to each of the red flags listed in the Haas article, Dr. McCandless testified: "When I look through this list, I don't really see a single thing on the list of cardinal findings, of red flag findings, that A.S. has." Tr. at 370.

Haas also noted that "there are a multitude of nonspecific symptoms that frequently occur in children with mitochondrial disease but have a broad differential diagnosis, and more often lead to other clear diagnoses."[9] Haas at 1327. With respect to these nonspecific symptoms, Dr. McCandless opined that A.S. experienced failure to thrive, infantile spasms, intractable epilepsy, and chronic unexplained constipation or diarrhea. Tr. at 371. He went on to note that "Seizures, intellectual disability, poor feeding and constipation are all extremely common findings in children with brain abnormalities for any reason, and they are in no way specific or strongly suggestive of primary mitochondrial disease in this child." First McCandless Rep. at 6.

Dr. McCandless also noted that A.S.'s growth suggests that she does not have mitochondrial dysfunction. He testified as follows:

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[8] *Dorland's*, www.dorlandsonline.com/dorland/definition? id=12929 (last accessed February 2, 2022).

[9] This list of nonspecific findings includes: failure to thrive, short stature, intrauterine growth retardation, microcephaly, hypotonia, infantile spasms, intractable epilepsy, unexplained movement disorder, hearing loss, axonal neuropathy, status epilepticus with an additional red flag or nonspecific feature, coma, ototoxicity to certain medications, tachycardia, optic nerve hypoplasia, pigmentary retinopathy, chronic or cyclic vomiting, chronic unexplained constipation or diarrhea, symmetric lipomatosis, hypothyroidism, hypoparathyroidism, idiopathic growth hormone deficiency, renal tubular dysfunction, nephrotic syndrome, unexplained basal ganglia lesions, unexplained central nervous system atrophy, unexplained leukodystrophy, sudden infant death syndrome, multigenerational maternal inheritance pattern of migraine headaches, depression, or anxiety disorder. Haas at 1328.

> [I]f you have significant mitochondrial dysfunction, by definition, you have a decrease in the efficiency of utilizing the energy you're taking in from the food you eat, and the fact that A.S. continued to gain weight in spite of the fact that she was at this point taking in less than the minimum expected amount of calories to support growth and development suggests that she was using those calories very efficiently. She just wasn't able to get enough of them in because of her neurological dysfunction.

Tr. at 338. This point strengthens Dr. McCandless' overall opinion that A.S.'s clinical picture is not consistent with mitochondrial dysfunction. In analyzing the Haas article, I find that while A.S. does have some findings that can be associated with mitochondrial disease or dysfunction, her overall clinical picture, discussed in more detail below does not support this diagnosis.

In addition to his testimony concerning the Haas article, Dr. Boles also spent a significant portion of his testimony discussing A.S.'s blood and urine testing.

1. Blood, Urine, and CSF Testing do not Support Mitochondrial Dysfunction in A.S.

Dr. Boles opined that A.S.'s abnormal blood and urine testing results constituted a constellation of findings that when considered in their totality, were "highly specific for mitochondrial dysfunction." Tr. at 109. As discussed in more detail below, I do not agree with Dr. Boles' conclusion.

a. *Plasma Lactate*

Dr. Boles noted that A.S.'s plasma lactate levels were mildly elevated three times in June of 2012 (18.8, 19.5 and 22.3 mg/dl (normal <18)). Boles Rep. at 7; Tr. at 106; *see* Ex. 5 at 192. He testified that one elevation would not be concerning, but three elevated levels are "consistent with mitochondrial dysfunction and suggestive thereof." Tr. at 108. Dr. Boles further testified that "I could only find three elevated -- I could only find three lactate determinations in the chart and all three of them were elevated." *Id.* In fact, A.S.'s plasma lactate levels were measured in the normal range at 9mg/dL in January of 2013. Ex. 11 at 946; Ex. 5 at 192. The record in this case is devoid of any explanation of this normal plasma lactate level and how it relates to mitochondrial dysfunction in A.S.

Dr. McCandless disagreed with Dr. Boles' testimony concerning the significance of A.S.'s mildly elevated plasma lactate levels. He stated that standard practice in a children's hospital is to use a tourniquet to draw blood. Tr. at 346. This procedure results in "trivial elevations of lactate" as seen in A.S.'s case. *Id.* at 345. Dr. McCandless testified further on this point:

> In our clinical practice in Cleveland, we did an extensive analysis of lactate values, comparing them to patients that eventually ended up with a diagnosis of mitochondrial disease and those who did not. What we found is the patients that ended up with a diagnosis of mitochondrial disease … -- that the lactates were elevated, but they were at least 150 percent of the upper limit of normal of … the reference range for that laboratory. And so our practice there … was that we did

> not consider a lactate significantly elevated as being informative for mitochondrial disease unless it was greater than 150 percent of the upper limit of normal in that laboratory.

Tr. at 346.

I note that an article filed by Petitioners supports the point that A.S.'s plasma lactate levels were not abnormally elevated so as to raise a concern for mitochondrial dysfunction. *See* Edmonds et al., *The Otolaryngological Manifestations of Mitochondrial Disease & the Risk of Neurodegeneration with Infection*, 128 ARCHIVES OF OTOLARYNGOLOGY–HEAD & NECK SURGERY 355-62 (2002) (filed as Ex. 24) (hereinafter "Edmonds"). The Edmonds article evaluated 40 patients with mitochondrial disease. In order to be enrolled in the study, patients had to meet two requirements: 1) lactic acid levels in the blood or CSF of 30 mg/dL or greater; and 2) an objective defect in the mtDNA or oxidative phosphorylation. Edmonds at 356. A.S. met neither of these requirements. With respect to plasma lactate levels, none of A.S's levels exceeded 30 mg/dL. While this point is not dispositive on the question of whether A.S. has mitochondrial dysfunction, it does constitute further evidence suggesting she does not. I find that Dr. McCandless is persuasive on this point, and that A.S.'s mildly elevated plasma lactate levels are not consistent with mitochondrial dysfunction, but instead likely represent mildly elevated levels that result from the use of a tourniquet.

b. *Urine Organic Acids*

Dr. Boles discussed the urine organic acids, noting that on June 25, 2012 these levels were read as "non-specific." He noted however, that "there were several elevations, including in pyruvate 75 (normal 0-34), succinate 127 (normal 18-79…), citrate 1696 (75-667…), suberic 3 (0-2 …), and glutarate 4 (0-2…)." Boles Rep. at 7-8; Ex. 11 at 1937.

In discussing pyruvate, Dr. Boles noted that A.S.'s pyruvate level was 75, where the normal range is between zero to 34. Tr. at 110. Based on this, he stated that A.S.'s pyruvate level was approximately double the upper limit of normal. *Id.* Dr. Boles further opined as follows: "I would consider that elevated pyruvate to be a fairly good indicator of mitochondrial dysfunction, not proof in itself, but an important part of the constellation that I'm building to suggest that the entirety of the symptoms and signs suggest mitochondrial dysfunction." Tr. at 110.

Dr. McCandless disagreed. He opined that A.S.'s pyruvate did not reach a level suggestive of mitochondrial disease or dysfunction. Tr. at 346-47. He noted that "very few metabolic specialists even think about the measurement of pyruvate in urine organic acids." *Id.* at 350. Dr. McCandless again provided persuasive testimony based on his experience running a laboratory. He testified as follows:

> And when you do the urine organic acid test, one of the things you do in preparing the samples, you add a very strong base solution to the sample, and it totally screws up the relationship of the lactate and pyruvate. So to say that there's a modest elevation of pyruvate means nothing in the urine organic acid, and anyone who runs

> a urine organic acid laboratory knows this. So the pyruvate is just -- it's just not meaningful.

Tr. at 350-51.

Dr. McCandless also discussed several other organic acids that were mildly increased, to include oxalic acid and fluorophenylacetic acid, glycine and hexanoylglycine. He noted that these levels may be related to overgrowth of gut bacteria, which he described as "a common thing that one sees in people with neurologic disorders who have constipation." Tr. at 347.

With respect to glutaric acid, which Dr. Boles noted as elevated in his report (tested at 4 with a normal range of 0-2), Dr. McCandless again opined that this result was not significant. "I'll tell you, as someone who has done this test in the lab for almost 20 years, there is no difference between four and two in these numbers. They are the same. That is not a significant difference. And to try to interpret this lab to that degree of specificity is a gross overcall." Tr. at 349.

Dr. Boles highlighted A.S.'s succinate level, which was 127 where the normal range extends up to 79. Tr. at 110. Dr. Boles opined that this level shows an abnormal and fatty acid metabolism. *Id.* In disagreeing with Dr. Boles, Dr. McCandless testified as follows: "Succinic acid is well known to go up and down and to be often very elevated. It can be elevated in people that have mitochondrial disease, but it's usually markedly elevated. It's one of the largest peaks on the chromatogram, and that is not the case in this sample." *Id.* at 351.

Dr. Boles discussed suberic acid in his report and at hearing, noting that it was mildly elevated. Tr. at 111. Dr. McCandless testified that "it's well documented in the literature, since the late 1980s, that suberic acid is a commonly seen finding in children that are on special formulas, like that have medium chain fats in them, or when children are fasting. So suberic acid is typically a marker for fasting." *Id.* at 352.

Dr. McCandless additionally noted that A.S. did not have elevated levels of 3-methylglutaric acid (3MG) or 3-methylglutaconic acid, which are generally elevated in individuals with mitochondrial dysfunction. Tr. at 352.

In sum, while some of A.S.'s urine organic acid levels were elevated, Dr. McCandless persuasively explained that these elevations did not support that A.S. suffers from mitochondrial dysfunction.

c. *Plasma Acylcarnitines*

A.S.'s October 24, 2013 testing revealed mild elevations in C2, a fatty acid called acetylcarnitine (21.54, normal 2.79-16.23), C3DC, C4OH, and C5OH metabolites. Ex. 2 at 41. With respect to these numbers, Dr. Boles opined that "while there are various reasons why those metabolites can be elevated, the constellation of all of those metabolites being elevated, in my mind, strongly suggests mitochondrial dysfunction." Tr. at 113.

Dr. McCandless opined that analysis of acylcarnitine is not especially informative concerning mitochondrial disorders. Tr. at 353. He further stated "[t]his is the pattern we see in the lab every day on patients who are taking supplemental carnitine." *Id.* At the time of this test, A.S. was in fact taking supplemental carnitine. *See* Ex. 2 at 11.

Dr. McCandless also made the compelling point that during A.S.'s initial hospital admission on June 22, 2012, when she was at her sickest, her acylcarnitine levels were normal. *See* Ex. 11 at 2362. This same test measured her total carnitine at 46, which is below the reference interval, but according to Dr. McCandless "well within the normal range." Tr. at 357; Ex. 11 at 2364. He testified that "[i]ndividuals who are sick, who are acutely ill or just not feeding very well, their carnitine will always be low. I don't consider a total carnitine significantly low until it's below 15 or 20." Tr. at 357.

d. *Methyltetrahydrofolate*

Dr. Boles noted that A.S.'s methyltetrahydrofolate level was in the low end of normal (41) when tested on November 4, 2013; normal range is between 40-197. Tr. at 120. Dr. Boles testified that "[t]he methyltetrahydrofolate is low or low normal in many cases of mitochondrial dysfunction. However, it is nonspecific and it is simply one of many different indications in terms that there might be mitochondrial dysfunction in this patient." Tr. at 121.

Dr. McCandless disagreed with Dr. Boles, and noted that although people with mitochondrial disease can have low methyltetrahydrofolate levels, this particular test will also return low in people that have seizures. Tr. at 365. He testified that "almost -- every sample I've ever sent for that test, that is low, and that's because we do the test in people with seizures, and it's well known that that test will be low in people that have seizures." *Id.* A.S. was experiencing seizures at the time this test was performed. Because of that, Dr. McCandless opined that the low result was not indicative of mitochondrial dysfunction or disease. *Id.*

Ultimately, I do not find that A.S.'s plasma lactate, urine organic acid, acetylcarnitine, or methyltetrahydrofolate levels are indicative of mitochondrial disease or dysfunction. In arriving at this determination, I have credited the opinion of Dr. McCandless over that of Dr. Boles.

2. Buccal Swab Testing Does Provide Some Minimal Support for Mitochondrial Dysfunction in A.S.

The results of buccal swab testing received on November 27, 2012 note that "A.S. may have a significant deficiency in the respiratory complex IV activity of the bucca mitochondria." Ex. 7 at 35. Dr. Boles testified that buccal swab testing is the gold standard for diagnosing mitochondrial dysfunction and that these results "prove[] mitochondrial dysfunction in this child." Tr. at 113, 114.

Dr. McCandless disagreed with Dr. Boles and testified that buccal swab testing is not "widely accepted by mitochondrial experts as having significant value." Tr. at 358. One reason for this is the lack of published data that show how stable the mitochondrial enzymes are after a saliva sample is collected and then shipped to the laboratory. Tr. at 360.

Dr. McCandless further noted that there is only one piece of medical literature on this testing, and the article was written by the inventor of the test. *Id.* Importantly, the literature does not provide the validation data that, according to Dr. McCandless, "a laboratory would need for proposing a diagnostic test." *Id.* at 359.

Dr. McCandless additionally criticized the test due to its lack of specificity. He indicated that he can't find that the specificity of the test has ever been published. In terms of the significance of this lack of specificity, he testified as follows:

> When you're looking for a diagnosis and you do a test, most of the people you do your test on are going to be normal … it looks positive even though they don't have the disease -- and you do that test thousands of times, and most of the people that you do the test on don't have the disease, what that means is that most of the positive tests will be false-positives. So a test like this cannot be used for diagnostic purposes until that … positive predictive value of the test is known and published, and that is not known for this test.

Tr. at 359-60.

Dr. McCandless also discussed the particulars of A.S.'s sample. He testified that there is a normal range of protein you should see in a buccal swab sample. This range is between 350 to 1000 micrograms. Tr. at 361. A.S.'s sample had 160 micrograms of protein, which "means every value in that sample should be questioned even more carefully." *Id.* In the testing process, the citrate synthase is divided by the protein measurement. *Id.* at 362. Dr. McCandless noted that "if the protein measurement you're using is outside the control range, it means that you're amplifying the inherent error in the measurement." *Id.*

Ultimately, Dr. McCandless opined that the buccal swab test is like a screening test and can constitute "an indicator that you should consider doing more testing." Tr. at 361. I find Dr. McCandless to be persuasive on this point. A.S.'s buccal swab testing constituted some evidence suggesting further inquiry into whether A.S. had mitochondrial dysfunction was appropriate. Standing on its own, it does not preponderantly establish that A.S. did have such dysfunction.

3. A.S.'s Mitochondrial DNA Sequence does not Support Mitochondrial Dysfunction

In his report, Dr. Boles stated that A.S.'s mitochondrial DNA sequence was read as normal, but he opined that "there are two rare variants that cannot be said to be either definitely "benign" or "disease related," and thus are better defined as "variants of uncertain significance": 5298A>G, p.Ile277Val in the *ND2* gene (present in 4/6391 people), and 5913G>A, Asp4Asn in the *CO1* gene (present in 27/6391 people)." Boles Rep. at 8. At hearing, Dr. Boles testified that over time it was discovered that the NDUFA1 variant was too common and not disease linked, so it would be interpreted as a benign variant today. Tr. at 131.

Dr. McCandless opined that neither molecular variant in A.S.'s mitochondrial DNA is likely associated with mitochondrial disease. Dr. McCandless stated that the NDUFA1 variant is present in A.S.'s father, who is unaffected by it. Dr. McCandless further explained that "this gene is on the X chromosome, of which males have only one copy, and females two. It is a generally accepted principal of clinical genetics that an X chromosome variant that does not cause disease in a male is not a reasonable explanation for disease in a female." First McCandless Rep. at 5. Further, after they issued their report, the laboratory that did the testing discovered that this variant was benign. Tr. at 369.

Dr. McCandless noted that her other variant involves a gene "that if you have both copies broken causes a condition called methylmalonic acidemia. She does not have methylmalonic acidemia. Her metabolites … very clearly prove that." Tr. at 367.

Ultimately, we know A.S.'s mitochondrial DNA sequence, and this information does not support mitochondrial dysfunction in A.S.

4. MRI Imaging does not Support Mitochondrial Dysfunction in A.S.

Dr. McCandless opined that if there "was an acute and severe failure of mitochondrial function, one would reasonably expect to see MRI changes." Third McCandless Rep. at 2. A.S.'s MRIs from June 21, 2012, January 18, 2013, and December 18, 2013 showed no evidence of parenchymal abnormality. *See* Ex. 11 at 2328; 255, 976. Dr. McCandless opined that the lack of findings on MRI does not, standing alone, rule out mitochondrial dysfunction; however, it constitutes "one more argument against that diagnosis." Third McCandless Rep. at 2. Dr. Wiznitzer agreed, stating "[t]he normal MRI and EEG findings during her June 2012 hospital admission are consistent with the conclusion that she did not have an acute encephalopathy with impairment of consciousness and that her neurological dysfunction was not caused by mitochondrial dysfunction." Third Wiznitzer Rep. at 4.

In an article filed by Petitioners, Dr. Andrea Gropman discussed neuroimaging in cases of mitochondrial disease. She noted that "common patterns of brain MR imaging can be identified in patients with mitochondrial disorders." Andrea L. Gropman, *Neuroimaging in Mitochondrial Disorders*, 10 NEUROTHERAPEUTICS 273-85, 284 (2013) (filed as Ex. 60) (hereinafter "Gropman"). This article supports Respondent's position that regression caused by mitochondrial disease should be visible on MRI. The fact that A.S.'s MRIs were normal is further evidence that she did not have a mitochondrial dysfunction.

5. A.S.'s Treating Physicians

Several of A.S.'s treating physicians questioned whether A.S. had mitochondrial dysfunction. For example, Dr. Fran Kendall noted at an appointment on March 6, 2013 that "the NDUFA-1 variant is likely the cause of her issues." Ex. 10 at 4. At the time of this appointment, Dr. Kendall did not know that the NDUFA-1 variant was benign. The fact that one premise of Dr. Kendall's opinion was incorrect undercuts the weight that I have afforded it. In addition, citing to the buccal swab test results, Dr. Kendall stated that "buccal swab mito enzyme screening studies were notable for signs of mito proliferation and complex IV deficiency." *Id.* For the reasons

discussed earlier in this decision, I do not find this opinion regarding buccal swab testing to be persuasive.

On February 11, 2013, A.S. and her parents had a genetic consultation with Dr. Vidya Krishnamurthy, who assessed A.S. with a mitochondrial metabolism disorder. Ex. 7 at 60-61. Like Dr. Kendall, Dr. Krishnamurthy also based his assessment on an incorrect interpretation of the NDUFA1 variant. He further noted that buccal swab testing "showed complex IV deficiency but needs to be retested." *Id.* at 60.

Although Drs. Kendall and Krishnamurthy both considered that A.S. suffered from mitochondrial dysfunction, neither provided an updated opinion once the NDUFA1 variant was identified as benign. Further, in examining A.S.'s more recent medical records, her treating doctors do not refer to mitochondrial disease. A.S. is no longer receiving carnitine treatment for mitochondrial diseases. This suggests her treating doctors do not believe she suffers from that condition.

Additionally, Dr. McCandless noted that her neurologist, Dr. Nayak, treated A.S. with valproic acid. *See* Ex. 53 at 194. He testified that "[n]o neurologist that I know, no respectable neurologist, would ever put a patient they believed has mitochondrial disease on Depakote, on valproic acid, because that is a known danger … that is well known to cause liver failure in kids with mitochondrial dysfunction." Tr. at 372-73. The fact that Dr. Nayak treated A.S. with valproic acid is strong evidence of his belief that she did not suffer from mitochondrial dysfunction.

In evaluating the evidence on this issue, to include the medical records, the testing results, and the expert opinions, I find that Petitioners have not presented preponderant evidence that A.S. suffers from mitochondrial disease or dysfunction.

B. *Loving* Prong One: A.S.'s Condition Prior to the June 18, 2012 Vaccinations

Prior to the June 18, 2012 vaccinations, A.S. was experiencing a severe neurologic dysfunction such that the evening after her six-month well visit, Petitioners were "up all night processing" and researching on the internet. Ex. 8 at 3. A.S. was not taking in enough calories, likely due to an underlying neurologic issue which resulted in tongue thrusting. Ex. 8 at 5; Tr. at 261. Since birth, she had taken up to one hour to feed. Ex. 11 at 2188. She had lost the ability to consistently roll over. Ex. 8 at 4. She was "always stiff" and exhibited foot and hand clenching. *Id.*; Ex. 3 at 1. At five months of age, she began focusing on Mrs. Svagdis' face less. She displayed decreased eye contact and an increased progressive tendency to zone out. Ex. 3 at 1.

C. *Loving* Prong Two: A.S.'s Condition after the June 18, 2012 Vaccinations

After her June 18, 2012 vaccinations, Petitioners followed the recommendation Dr. Douglas made during the six-month well visit and scheduled an appointment with a neurologist. Dr. Cheng evaluated A.S. on June 20, 2012 and told Petitioners "there's a hospital right there, walk over there, go now, it would be faster than an ambulance." Tr. at 37. A.S. was admitted to CHOA. She continued a downward trend in calorie consumption, consuming under two ounces while feeding. She had an NG tube placed on June 22, 2012. After that, her "[d]isposition and interaction

[] markedly improved on full feeds." Ex. 11 at 2264. EEGs on June 20 and June 22, 2012 were normal.

A.S. was admitted to CHOA in November of 2012 and had an abnormal EEG. She was found to be "at risk of having recurrent unprovoked seizures." Ex. 11 at 1234. As a result, she was started on Trileptal. *Id.* A.S. began having paroxysmal episodes in November of 2012. Ex. 11 at 1235-37. She developed infantile spasms in December of 2012, which were well controlled with Topamax.

As of August 14, 2014, when she was approximately 32 months of age, A.S.'s development was tested at about the 10 month level. During this visit, Dr. Flamini noted that A.S. "makes noises, still won't swallow and is tube fed." She was noted to be "sitting independently with lateral protective reflexes, not up on all 4's." Ex. 2 at 1. Her condition at the time of the entitlement hearing remained substantially the same as what Dr. Flamini observed in August of 2014. *See* Tr. at 55.

D. *Loving* Prong Three: Did A.S. Experience a Significant Aggravation of her Condition?

A.S.'s deterioration is consistent with the Vaccine Act's definition of significant aggravation resulting in markedly greater disability, pain, or illness accompanied by substantial deterioration of health. § 33(4). Therefore, this leaves the question of whether that significant aggravation was vaccine-related.

E. *Loving* Prong Four/*Althen* Prong One: Petitioners have not Established a Reliable and Reputable Theory Concerning How the Vaccinations A.S. Received Can Cause the Significant Aggravation of A.S.'s Underlying Neurologic Condition

Under *Loving* prong four/*Althen* prong one, the causation theory must relate to the injury alleged. Thus, petitioners must provide a "reputable" medical or scientific explanation, demonstrating that the vaccine received can cause the type of injury alleged. *Pafford,* 451 F.3d at 1355-56. The theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen v. Sec'y of Health & Hum. Servs*., 35 F.3d 543, 548 (Fed. Cir. 1994). It must only be "legally probable, not medically or scientifically certain." *Id*. at 549.

Petitioner's theory that the vaccines A.S. received "can cause" a significant aggravation of her pre-existing condition can be summarized as follows: A.S. has an underlying mitochondrial dysfunction; vaccination caused cytokine production; these cytokines crossed the blood-brain barrier and were produced at a high enough level to result in overwhelming oxidative stress; because mitochondrial DNA are particularly susceptible to oxidative stress, this stress resulted in cell death, which in turn caused progressive insults to the brain. *See* Pet'r's Post Hearing Brief at 9. The vaccines ultimately caused "neuro intra-brain damage or encephalopathy" that eventually resulted in infantile spasms (approximately five months later). Tr. at 175-76. (Dr. Kinsbourne testified that "In this case, there was no evidence of epilepsy at the onset of the vaccine injury. However, the brain damage that resulted from it in the longer term did result in seizures and specifically in infantile spasms.") Tr. at 163.

Other Vaccine Program cases have considered and rejected this theory. *See Kreizenbeck v. Sec'y of Health & Hum. Servs.*, No. 08-209V, 2018 WL 3679843, at *31 (Fed. Cl. Spec. Mstr. June 22, 2018) (finding Dr. Kinsbourne's opinion regarding the ability of vaccines to cause oxidative stress and ensuing immune dysfunction to be "weakly grounded in reliable science."); *Pope v. Sec'y of Health & Hum. Servs.*, No. 14-078V, 2017 WL 2460503, at *20 (Fed. Cl. Spec. Mstr. May 1, 2017) (finding that petitioners did not offer a reliable causation theory that vaccines could precipitate an encephalopathic event in a person with mitochondrial dysfunction resulting in developmental regression); *Miller v. Sec'y of Health & Human Servs.*, No. 02-235V, 2015 WL 5456093 (Fed. Cl. Spec. Mstr. Aug. 18, 2015) (concluding that petitioners failed to demonstrate that several childhood vaccines caused encephalopathy or aggravated underlying mitochondrial disease/dysfunction).

At the outset, I note that several studies have documented the safety of vaccines in individuals with mitochondrial enzyme deficiencies. *See* Morgan, et al., *Vaccines Are Not Associated With Metabolic Events in Children With Urea Cycle Disorders*, 127 PEDIATRICS 5, 1147-53 (2011) (filed as Ex. K, Tab 4); Klein, et al., *Evaluation of Immunization Rates and Safety Among Children With Inborn Errors of Metabolism*, 127 PEDIATRICS 5, 1139-46 (2011) (filed as Ex. K, Tab 3); Barshop & Summar, *Attitudes regarding vaccination among practitioners of clinical biochemical genetics*, *95* MOLECULAR GENETICS AND METABOLISM 1-2 (2008) (filed as Ex. K, Tab 1). These studies support the point that even if A.S. did suffer from an underlying mitochondrial disorder, this condition did not make her more susceptible to vaccine-induced injury.[10]

It is important to note that Petitioner's expert immunologist linked his causation opinion to the existence of A.S.'s underlying mitochondrial dysfunction. Dr. Gershwin testified at hearing as follows: "[I]f it turns out that A.S. does not have a mitochondrial defect, then my plausible -- what I think are plausible explanations of what happened would not be offered in this courtroom." Tr. at 200. Because I have found that A.S. does not have mitochondrial dysfunction, this portion of Petitioners' theory is unsupported. Several other components of Petitioners' theory are also unsupported.

[10] Although not discussed by any expert in the case, I also considered the case report filed by Petitioners involving Hannah Poling. *See* Jon S. Poling et al., *Developmental Regression and Mitochondrial Dysfunction in a Child With Autism*, 21(2) J. CHILD NEUROLOGY 170 (2006) (filed as Ex. 27) (hereinafter "Poling"). The case report noted: "This patient exemplifies important questions about mitochondrial function in autism and developmental regression.... If such [mitochondrial] dysfunction is present at the time of infections and immunizations in young children, the added oxidative stresses from immune activation on cellular energy metabolism are likely to be especially critical for the central nervous system, which is highly dependent on mitochondrial function. Young children who have dysfunctional cellular energy metabolism therefore might be more prone to undergo autistic regression between 18 and 30 months of age if they also have infections or immunizations at the same time. Although patterns of regression can be genetically and prenatally determined, it is possible that underlying mitochondrial dysfunction can either exacerbate or affect the severity of regression." In the case report, Poling questions whether vaccination triggers autistic regression in children with underlying mitochondrial dysfunction. I find that this single case report does not demonstrate that this occurs in cases of autism and does not speak to any other conditions.

1. There is not Preponderant Evidence that Cytokines Resulting from Vaccination Would be Produced at High Enough Levels to Cause the Damage Alleged

It is well established in the Vaccine Program that vaccination does promote the production of cytokines. However, Dr. McCusker noted that post-vaccination cytokines are produced at an extremely low level. First McCusker Rep. at 6. She persuasively opined that "[t]here is no evidence that low levels of peripheral cytokines released during vaccination result in pathological increases in CNS [central nervous system] cytokines." *Id.* at 7.

Dr. McKusker cited Kashiwagi et al. as support for this point. Kashiwagi et al., *Production of inflammatory cytokines in response to diphtheria-pertussis-tetanus (DPT), haemophilus influenzae type b (Hib), and 7-valent pneumococcal (PCV7) vaccines*, 10 HUMAN VACCINES & IMMUNOTHERAPEUTICS 3, 677–85 (2014) (filed as Ex. J, Tab 8) (hereinafter "Kashiwagi"). Kashiwagi examined the cytokine production in children after vaccination by measuring specific cytokine levels in serum. They demonstrated that IL1β , IL6, and TNFα were all detected at low levels. According to Dr. McCusker, "These data suggest that cytokines are produced and released by the peripheral immune system during vaccination but there is no evidence to suggest that the levels are sufficient to influence the development of cytokine-mediated changes in seizure thresholds as hypothesized by Petitioner's Expert." First McCusker Rep. at 6.

Dr. Kinsbourne referenced Dubé et al. in support of his opinion. *See* Dubé et al., *Interleukin-1β Contributes to the Generation of Experimental Febrile Seizures,* 57 ANN NEUROL. 1, 152-55 (2005) (filed as Ex. 17) (hereinafter "Dubé"). Dubé examined the role of IL1β in febrile seizures, specifically whether the infusion of IL1β into the lateral cerebral ventricles of mice would lower the seizure threshold. Dr. Kinsbourne noted that this study showed that IL1β injected into normal mice caused seizures, and that mice lacking the IL1β receptor were resistant to seizures. First Kinsbourne Rep. at 6. According to Dr. Kinsbourne, "[t]his work made it clear that an etiologic agent can provoke seizures regardless of whether a febrile reaction occurred." *Id.* While Dr. McCusker acknowledged that extremely high dose cytokine levels infused directly into the brain may lower the seizure threshold in mice, she emphasized the significance of the fact that "the amounts of cytokines required to induce this lowering of seizure thresholds in mice were more than 1000X greater than those found post vaccination in humans." First McCusker Rep. at 6. Dr. McCusker persuasively opined that vaccination does not result in significant cytokine changes in the brain. Accordingly, the Dubé article does little to advance Petitioners' position.

Ultimately, I am not convinced that cytokines produced following vaccination can result in the neurologic damage in the manner alleged in this case.

2. There is not Preponderant Evidence that a Mitochondrial Disorder Would Cause Mitochondria to Aberrantly Respond to Cytokines Resulting in Cell Death

Dr. Gershwin opined that because of her genetic mitochondrial defect, "[A.S.] would be more susceptible to cytokine production than a normal child who does not have mitochondrial dysfunction." Gershwin Rep. at 2. He opined that "in the presence of mitochondrial dysfunction, which will lead to alteration in ATP production, increased production of reactive oxygen species,

calcium dysregulation, and mitochondrial DNA damage, then her brain would be more susceptible to damage." *Id.* He specifically hypothesized that as a result of A.S.'s mitochondrial dysfunction, cytokine production would lead to worsening inflammation. *Id.*

Dr. Gershwin cited several articles in support of his causation opinion. He cited to Wenceslau et al. *See* Wenceslau et al., *Mitochondrial damage-associated molecular patterns and vascular function*, 35 EUROPEAN HEART JOURNAL 1172-77 (2014) (filed as Ex. 39) (hereinafter "Wenceslau"). This article focuses on "evidence linking [mitochondrial] DAMPs and immune system activation to vascular dysfunction and cardiovascular disease." Wenceslau at 1172. While this article does support the position that cell death leads to the release of DAMPS and immune system activation, it does not discuss the effects of cytokines on the mitochondria in patients with normal or abnormal mitochondrial activity. *Id.* at 1173.

Dr. Gershwin also cited to LeDoux et al. *See* LeDoux et al., *Mitochondrial DNA Repair: A Critical Player in the Response of Cells of the CNS to Genotoxic Insults*, 145 NEUROSCIENCE 4, 1249-59 (2007) (filed as Ex. 40) (hereinafter "LeDoux"). This article discusses the mechanisms of how normal functioning mitochondria can play a role in neurodegeneration. The authors discuss that cytokines can be involved in cell damage after ischemic insults or demyelinating diseases. LeDoux does not discuss genetic mitochondrial defects.

Sandireddy et al. is an article that discusses diabetic neuropathy. Sandireddy et al., *Neuroinflammation and Oxidative Stress in Diabetic Neuropathy: Futuristic Strategies Based on These Targets*, INTERNATIONAL JOURNAL OF ENDOCRINOLOGY (2014) (filed as Ex. 43) (hereinafter "Sandireddy"). In this article, the authors propose one potential theory to explain the cell damage which leads to diabetic neuropathy; specifically that mitochondrial dysfunction may cause increased oxidative stress and subsequent neuroinflammation. Sandireddy at 1. Sandireddy discusses the theory that oxidative stress results in cytokine production, not that cytokine production causes oxidative stress. *Id.* I do not find that this article provides support for Petitioners' theory that A.S.'s dysfunctional mitochondria resulted in an aberrant response to vaccination-induced cytokines.

Krysko et al. examined the "significance of mitochondrial DAMPs and … their contribution to inflammation and development of human pathologies." Krysko et al., *Emerging role of damage-associated molecular patterns derived from mitochondria in inflammation*, 32 TRENDS IN IMMUNOLOGY 4 (2011) (filed as Ex. 48) (hereinafter "Krysko"). The Krysko article shows that mitochondrial DNA can cause inflammation as a response to tissue injury. This article does not discuss the cytokine response in a patient with mitochondrial dysfunction.

In Verri et al., the authors suggested that "compromised mitochondrial function contributes to the aging process" and can increase the risk of developing Alzheimer's disease. Verri et al., *Mitochondrial Alterations, Oxidative Stress and Neuroinflammation in Alzheimer's disease*, 25 INTERNATIONAL JOURNAL OF IMMUNOPATHOLOGY AND PHARMACOLOGY 2 345-53 (2012) (filed as Ex. 45) (hereinafter "Verri"). Verri noted that dysfunctional mitochondria "contribute to reactive oxygen species" which can lead to oxidative damage and disease progression. Verri at 345. Verri discussed mitochondrial toxicity induced by β-amyloid. *Id.* While Verri does support the point that dysfunctional mitochondria contribute to reactive oxygen species, this point is a general one. Verri

also suggested that microglial release of cytokines in response to amyloid deposit stimulation can lead to neuro-dysfunction. The Verri paper was specific to Alzheimer's disease, which is not at issue in this case.

In sum, the medical literature cited by Dr. Gershwin does not provide persuasive support for his theory that mitochondrial dysfunction results in increased susceptibility to cytokines. As Dr. McCusker testified at hearing: "even if A.S. had these abnormal mitochondria, there's nothing in what was presented and what I've been able to find in the literature that says that in her brain, the presence of the cytokines would actually result in inflammation such that you will get a significant inflammatory change … and result in CNS deterioration." Tr. at 477. I agree with this assessment.

In arriving at my determination, I have considered the case of *Paluck v. Sec'y of Health & Hum. Servs.*, 786 F.3d 1373, 1379 (Fed. Cir. 2015). The petitioners in *Paluck* preponderantly demonstrated that the first signs of neurodegeneration occurred within several weeks of vaccination, that the record as a whole showed K.P.'s progressive neurodegeneration was consistent with his expert's medical theory, and further, that this medical theory was plausible. *Id.* at 1379. This case is substantially different from *Paluck*. In *Paluck*, the parties agreed there was a mitochondrial disorder, the causation theory was based on progressive neurodegeneration as opposed to "falling off a cliff", the parties filed different medical literature and relied on different experts, the MRI evidence indicated that K.P. "experienced progressive post-vaccination neurological deterioration" (*Id.* at 1385), the court found that "there was no credible evidence that [K.P.] suffered from any significant problems in his central nervous system" at the time of his vaccination (*Id.* at 1381), and the treating physicians opined that K.P.'s neurodegeneration had a toxic etiology, which could encompass vaccination. In the case at bar, I have found that A.S. does not suffer from mitochondrial dysfunction; inherent in Petitioners' causation theory is that A.S. fell off a cliff neurologically; A.S.'s MRIs were normal; A.S.'s pre-vaccination condition indicated severe neurologic decline; and A.S.'s treating physicians did not attribute her condition to vaccination.

Petitioners have not provided a sound and reliable medical theory connecting A.S.'s injury to the vaccines she received. Accordingly, Petitioners have not met their burden of proof regarding *Loving* Prong Four /*Althen* Prong One.

F. *Loving* Prong Five/*Althen* Prong Two

Loving prong five/*Althen* prong two requires the Petitioners to demonstrate a logical sequence of cause and effect that the vaccinations did cause a worsening of A.S.'s pre-existing condition. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375–77; *Capizzano*, 440 F.3d at 1326; *Grant*, 956 F.2d at 1148.

1. A.S. Experienced a Gradual Decline Beginning at around Four Months of Age

Throughout the hearing, Petitioners' experts opined that A.S.'s neurologic decline was rapid, beginning after vaccination. They repeatedly described A.S. as "falling off a cliff" developmentally. In fact, as Petitioners noted in their post hearing brief, "The 'rapid change in the

clinical manifestations following the vaccination[s]' is central to Petitioner's mechanism theory." Pet'r's Post-Hearing Brief at 10. Respondent contends that "[c]hildren with neurodegenerative disorders do not fall off a cliff. They evolve in their clinical presentation." Tr. at 307. For the reasons discussed below, I do not find that A.S.'s decline occurred in the manner described by Petitioners.

a. *Difficulty with Feeding Began before the Four Month Visit and Worsened through the Six-Month Visit*

The notes from A.S.'s four-month well visit indicate that she had some difficulty with feeding due to tongue thrusting. Ex. 8 at 5. Dr. Wiznitzer testified that "tongue thrusting tells us that you're not having good coordination of oral motor movements" which is regulated by the nervous system. Tr. at 261. He further noted that it took up to an hour for A.S. to feed. Tr. at 260; *see* Ex. 11 at 2188. Dr. Wiznitzer indicated that these points support the fact that A.S. already had neurologic dysfunction at the time of this four-month appointment. *Id.*

The record from the four-month well visit further documents that A.S. was consuming four ounces of formula six times per day for a total of 24 ounces of formula each day. Ex. 8 at 5. This is the equivalent of 90 calories per kilogram of weight per day. Tr. at 337. Dr. McCandless testified that this was "the absolute bottom of the normal range for supporting growth and development in an infant." *Id.*

During her six-month well visit, A.S. was taking three to four ounces of the same formula five times per day. The record notes that she was taking 45 minutes to finish this amount of formula. Ex. 8 at 4. Dr. Wiznitzer opined that this length of time to finish a small amount of milk demonstrated a "significant inefficiency in feeding." Tr. at 263. She was also eating homemade solids twice per day. *Id.* Dr. McCandless stated that A.S.'s caloric intake was significantly less than what she was taking at the time of her four-month visit. *Id.* at 337-38. The solid food that A.S. consumed was very low in calories. *Id.* Furthermore, Dr. McCandless calculated the milk intake to be "between 64 and 70 calories per kilo per day at a point in time where a typical infant would be taking between 100 and 120 calories per kilo per day to support … typical growth and development." *Id.* Ultimately, Dr. McCandless opined that A.S. experienced a worsening in feeding status which was "[v]ery clearly documented and worsening over several months." *Id.* at 338.

Dr. Wiznitzer described that A.S. was experiencing an evolution of her neurologic disorder. As she grew, she was unable to increase the number of calories she needed to take in, because she needed more at six months than she did at four months. Dr. Wiznitzer testified that as time goes on, "the inefficiency interferes with her ability to grow adequately, which is why she has the failure to thrive." Tr. at 280.

At a visit on June 22, 2012, Petitioners described to Dr. William Meyers at Children's Healthcare of Atlanta that A.S. had a recent decrease in feeding. The record noted that "Since 6/19/2012, her intake has shown a rapid decline in that at best she would take 3 ounces at a time, the next day 2 ounces at a time, and the next day only 1 ounce at best." Ex. 11 at 2189. The chronology provided by Petitioners suggested that A.S. began eating less the day after vaccination.

However, Dr. Wiznitzer noted that "When she made it to the hospital, if you look at her admitting weight, it was around what it was for the pediatrician. Had she not been feeding well at all during that two-day time period, I would have expected some weight loss from inadequate fluid intake." Tr. at 283. While I have considered Petitioners' description of A.S.'s reduced feeding the day after vaccination, I do not find that this change, if a change did occur, was attributable to the vaccines she received.

In assessing A.S. on June 22, 2012, Dr. Meyers noted that "she has crossed 2 standard deviations on the growth chart from her birth weight which was above the 15th percentile to an admitting weight which is now at the 2nd percentile for her age." Ex. 11 at 2191. This point supports a conclusion that A.S. developed problems with feeding beginning by four months of age, and that those problems led to decreased caloric intake and a reduced weight percentile.

b. *Decreased Focus/Tracking*

On June 18, 2012, at her six-month well visit, Dr. Douglas noted that A.S. still crossed her eyes; that this was "not significant at prior visits" but that "mom states noticing more since last visit." Ex. 8 at 4. Dr. Douglas further noted that A.S. exhibited "poor tracking" and that this finding was abnormal. *Id.*

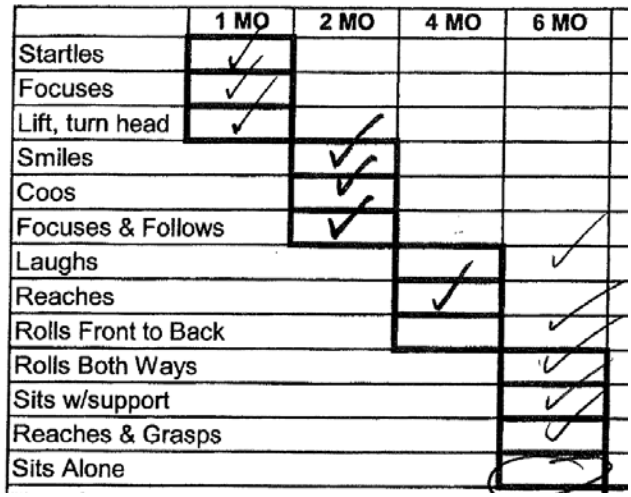
On June 19, 2012, A.S. visited Dr. Steven Lipsky, an ophthalmologist, at the Thomas Eye Group. Ex. 8 at 17. Dr. Lipsky noted that A.S. "does not fix and follow well, but when she is attentive, she does follow." *Id.* Dr. Lipsky further indicated that A.S.'s family has noted her eyes crossing since birth. *Id.* Dr. Lipsky opined that he felt that "her developmental status is way behind and her vision may very well be appropriate for her developmental state." *Id.*

The June 20, 2012 record from the visit with Dr. Meyers indicated that "According to the parents, the patient had been tracking up until 5 months of age but now has poor follow ability." Ex. 11 at 2189. Further, on June 20, 2012, Dr. Cheng (a neurologist) evaluated A.S. Ex. 3 at 1. Dr. Cheng's record indicated that "[i]n the past few weeks, there has been a progressive worsening of the tendency to "zone out." She stares up. There is very poor eye contact, even though mom is right in front of her talking to her." *Id.* Each of these records demonstrates that the worsening of A.S.'s poor eye contact and tracking began prior to her vaccinations.

c. *Loss of and Failure to Achieve Milestones*

During her six-month well visit, the record notes that A.S. was "not consistently rolling over now but has in past." Ex. 8 at 4. Dr. Kinsbourne acknowledged during the hearing that this constituted a regression. Tr. at 168-71. The fact that A.S. inconsistently performed a milestone that she had previously achieved is further support that her neurologic decline began before her vaccinations.

Preston Ridge Pediatric Associates created a chart of A.S.'s development at her six month well visit.



	1 MO	2 MO	4 MO	6 MO
Startles	✓			
Focuses	✓			
Lift, turn head	✓	✓		
Smiles		✓		
Coos		✓		
Focuses & Follows		✓		
Laughs				✓
Reaches			✓	
Rolls Front to Back				✓
Rolls Both Ways				✓
Sits w/support				✓
Reaches & Grasps				✓
Sits Alone				

Ex. 8 at 16: This chart demonstrates that at four months, A.S. was not achieving the milestones depicted in the bolded boxes, which included "laughs" and "rolls front to back". At six months, A.S. was not sitting alone. *Id.* The bolded boxes depict the milestones that should have been achieved at each given age. Tr. at 183. The fact that A.S. did not achieve these milestones on time demonstrates the continuing evolution of her clinical presentation.

d. *Changes in Tone*

During the six month well visit, Dr. Douglas noted that A.S. displayed "↑" tone in her four extremities and that her feet and hands were clenched. Ex. 8 at 4. Dr. Douglas additionally noted that A.S. had poor seated control and that she had "↓" upper body strength. *Id.* She indicated that both of these findings were abnormal. *Id.*

Petitioners aver that there was a dramatic change in A.S. between the date of her six-month well visit where she received her vaccines, and her presentation to Dr. Cheng on June 20th. They argue that several of Dr. Cheng's findings support their position, specifically his impressions, which included: spastic quadriplegia, suspected seizures/encephalopathy, global developmental delay, and failure to thrive. However, this position is belied by the medical records.

Importantly, Dr. Wiznitzer explained that a typical pediatrician would not use the same diagnostic terms as a neurologist. He testified that "it would be unusual -- highly unusual for a general pediatrician to diagnose either spastic quadriplegia or suspected seizures/encephalopathy." Tr. at 380. Dr. Wiznitzer and Dr. McCandless persuasively explained that although Dr. Douglas did not define A.S.'s presentation with the same terms that Dr. Cheng used, her observations of A.S. were virtually the same as Dr. Cheng's. For example, Dr. Douglas documented that A.S.'s four extremities had abnormal, increased tone. Dr. Cheng labeled this as spastic quadriplegia, which according to Dr. McCandless, "means increased tone in four extremities." Tr. at 408-09. According to Dr. McCandless, "those are the same thing." *Id.*

Respondent's experts persuasively opined that this increased tone in A.S.'s extremities did not develop in a matter of days. Dr. Wiznitzer testified, "Spasticity is never an acute reaction to a brain stressor." Tr. at 268. "So the fact that she's described as having spastic quadriplegia on June

20th tells me that whatever that is cannot be due to an insult to the brain from the vaccine, because spasticity would never be present two days after an insult." *Id.* Dr. McCandless made this point more emphatically when he said, "I would conclude that a diagnosis of spastic quadriplegia makes it impossible that it could be an acute change in the last 48 hours -- because that's not the course of spastic quadriplegia." Tr. at 381-82.

Dr. Cheng's records further support this point. Based on Mrs. Svagdis' history, Dr. Cheng noted that A.S. "always has both hands fisted" and that "[s]he is always very stiff." Ex. 3 at 1. This note demonstrates that the fisting of the hands and the stiffness are not new problems. Dr. Wiznitzer opined with respect to this issue:

> And the fact that she's always very stiff … -- he's not writing in his letter that she was not stiff two days ago and now she's stiff … -- if a parent reports that, you would write that down. He's writing down that she's always very stiff, which means that it has to have been there for some time.

Tr. at 273. Dr. Rowe's notes support increased tone in A.S. that predated vaccination. These records indicate that "Patient tends to keep arms flexed and hands in clenched position. (This has been going on for some time according to pictures mom has taken in the past.)" Ex. 11 at 2192.

A note in the medical record one day after A.S.'s six month well visit further supports this position. The handwritten note documenting a phone call on 6/19/2012 states, "Mom called [illegible] for call back this am to discuss well [visit] 6/18. Parents went home and researched on internet and up all night processing. … Appt this am with Dr. Lipsky at 9am. Unable to get appointment with Dr. Schuls until August. Mom requesting we call to get into neurologist due to significant changes developmentally/neuro since 4 mo[nth]s." Ex. 8 at 3. According to this note, Mrs. Svagdis reported significant developmental changes in A.S. since the age of four months.

Petitioners also argue that Dr. Cheng's impression on June 20, 2012 that A.S. suffered from global developmental delay was a new finding, and that the signs that led to this finding were not present during the six-month well visit on June 18, 2012. Dr. McCandless testified that global developmental delay is when you have "a developmental delay in at least two or more of four major areas of infantile development, which are fine motor, gross motor development, speech and language, and social." Tr. at 393. Gross motor refers to large muscle groups. *Id.* at 394. Dr. McCandless opined that Dr. Douglas' notes in the six month well visit record, which document increased tone in four extremities, hands clenched, and poor seated control constitute abnormal development in the gross motor skills category. *Id.* at 396. He further testified that A.S.'s deficit in "attentional engagement" was evidence of a delay in the social category. *Id.* at 394. In fact, Dr. Cheng's record from June 20, 2012 notes that "[t]here is very poor eye contact, even though mom is right in front of her talking to her." Ex. 3 at 1. Dr. Cheng further noted that this had been going on for "the past few weeks." *Id.* Based on this medical record evidence, Dr. McCandless opined that A.S. had global developmental delay on June 18, 2012. Tr. at 396. I agree with this assessment.

Ultimately, Dr. Wiznitzer persuasively testified that "There's no real major difference between the exam on the 18th and the exam on the 20th. So, therefore, there is no 'falling off the cliff.'" Tr. at 281.

2. A.S.'s Clinical Presentation on June 20, 2012 was not Consistent with an Encephalopathy or an Acute Brain Injury

During her hospitalization, A.S. had a normal EEG and a normal video EEG. Ex. 11 at 2279-80, 2173. These findings are not consistent with Petitioners' theory that A.S. "fell off a cliff" neurologically. As Dr. Wiznitzer noted at hearing: "If you're going to have dead neurons of sufficient number that would lead to the condition that she has today, … you would see changes on the EEG." Tr. at 285.

Similarly, A.S.'s MRI performed on June 21, 2012 was also normal. Ex. 11 at 2328. Again, Dr. Wiznitzer noted that the cell death sufficient to cause A.S.'s neurologic condition should result in changes on the MRI. Tr. at 286. "You should see abnormal signal from the white matter or from the gray matter of the brain in a damage pattern … and if you have cell … death, there should be atrophy. There should be loss of brain substance. It is not described on the MRI." *Id.* at 287. These three tests all provide additional evidence that A.S. did not suffer from an acute neurological condition.

Dr. Kinsbourne opined that A.S. did not have visible changes on EEG or MRI because she had a mitochondrial encephalopathy and not an encephalopathy caused by structural damage or trauma. Second Kinsbourne Rep. at 1. He stated that as a result, her affected neurons underperformed but that it took a long time for the resulting damage to be visible on MRI. *Id.*

Dr. Wiznitzer disagreed, noting that both mitochondrial and anoxic encephalopathies "lead to brain damage by the same end result – failure of adequate energy to support cellular function." Third Wiznitzer Rep. at 1. He opined that this permanent brain injury would be visible on EEG and MRI. *Id.* In support of his position, Dr. Wiznitzer cited to Omkar N. Markland, *Pearls, Perils, and Pitfalls in the Use of the Electroencephalogram*, 23 SEMINARS IN NEUROLOGY, 1, 7-46 (2003) (filed as Ex. O) (hereinafter "Markland"). The Markland article notes "There is a good correlation between the severity of the EEG changes, the severity of the encephalopathy, and the clinical state of the patient." Markland at 10. Markland also describes metabolic encephalopathies on EEG: "An EEG showing diffuse slowing of the background and presence of triphasic waves is highly suggestive of a metabolic encephalopathy." *Id.* at 11. The Markland article demonstrates that EEG is a valuable tool to measure encephalopathy, to include metabolic encephalopathy. Accordingly, I find it significant that A.S.'s EEGs were normal in June of 2012.

In addition to the normal testing, Dr. Rowe described A.S. as alert and interactive and indicated that she had a nontoxic appearance on June 21, 2012. Ex. 11 at 2205. According to Dr. Wiznitzer,

> You can't have an acute injury or worsening of condition to the brain due to the alleged mitochondrial dysfunction and resultant cell death that caused her neurologic picture to fall apart. That's not … consistent with neurology. You should be acutely encephalopathic. Encephalopathic means you would not be awake and alert. It means that at that time your EEG would show a slow background.

Tr. at 297-98. Dr. Rowe's description of A.S. also suggests that she did not suffer from an acute neurological decline.

A.S.'s normal EEGs, her normal MRI, and the fact that she was alert on June 21, 2012 all support the position that A.S. did not suffer from an acute brain injury.[11]

3. Petitioners Describe a Worsening in A.S.'s Condition Immediately after her Vaccinations on June 18, 2012

Petitioners noted to several medical providers that A.S. worsened following her June 18, 2012 vaccines. For example, on June 22, 2012, Petitioners described A.S.'s feeding after her vaccination as decreasing further than its already low level. Ex. 11 at 2189. Mrs. Svagdis told Dr. Bruce that A.S. experienced "a significant regression in milestones" since vaccination, noting that A.S. "will not even focus on mom, her cooing has decreased as has her appetite." *Id.* at 2193.

There are also several instances where Petitioners provided a medical history which ascribed causality to A.S.'s vaccines but were inconsistent with other more contemporaneous medical records. For example, the HPI section from the November 15, 2012 medical records indicates that A.S. "appeared to be doing very well until several hours after the administration of a series of immunizations on June 18, 2012 at 6 months of age when she developed lethargy, staring, anorexia, and abnormal upper extremity curling or posturing." Ex. 10 at 6. *But see* Ex. 8 at 5, 4 (documenting difficulty with feeding at four month and six month well visits); Ex. 3 at 1 (visit from June 20, 2012 describing that A.S. "always has both hands fisted", "is always very stiff", and "in the past few weeks" has shown a "progressive tendency to 'zone out.'"). Additionally, A.S. was admitted to the Cleveland Clinic Children's Hospital on January 3, 2013. The notes from this visit indicate that "within a few hours after receiving her 6 month[] shots, patient developed episodes of "stiffening" of both arms and legs; and was unable to roll and babble as she was previously able to do." Ex. 5 at 9. *But see* Ex. 8 at 4 (notes from medical visit on the day of vaccination where A.S. was not consistently rolling over and exhibited increased tone in her four extremities; Ex. 11 at 219-20, noting "Patient tends to keep arms flexed and hands in clenched position (this has been going on for some time according to pictures mom has taken in the past).").

Respondent's experts discussed Petitioners' perceptions regarding the onset of A.S.'s condition throughout the hearing. Both Dr. McCandless and Dr. Wiznitzer repeatedly endorsed Petitioners' sincere belief that A.S. had a precipitous decline post-vaccination. Dr. McCandless testified as follows:

[11] During the entitlement hearing, Dr. Kinsbourne noted that "In this case, there was no evidence of epilepsy at the onset of the vaccine injury. However, the brain damage that resulted from it in the longer term did result in seizures and specifically in infantile spasms." Tr. at 163. *See also* Tr. at 185. Inherent in my determination that A.S. did not develop immediate or near immediate worsening of her neurologic condition after her June 18, 2012 vaccinations is my conclusion that A.S.'s vaccines did not cause her to develop seizures or infantile spasms, which are not documented in the medical records until several months post-vaccination.

> That sense of an acute change often occurs when a physician or a group of physicians point out a variety of things that are not progressing as expected. So to the parents, it does feel -- it feels like a very acute and abrupt change. They went in one hour from having a normal baby to having a baby that had all kinds of health problems and neurological developmental problems, that needed to see two specialists very soon. If you're a parent and you go from a baby that to you is completely normal one day to two days later a baby that you're told to carry across the street because they have to be admitted for a workup, that is a huge change. That feels like you've just fallen off a cliff. And it's not that A.S. fell off the cliff. There's plenty of evidence that she had an evolving picture of neurological dysfunction … but to the parents, it must have felt like they had fallen off a cliff.

Tr. at 335-36. I find the testimony of Drs. Wiznitzer and McCandless to be persuasive. These observations, based on years of treating patients who have similar conditions as A.S., explain why Petitioners' views concerning the onset of A.S.'s condition are at odds with the majority of the contemporaneous medical records. For the reasons discussed in this decision, I find that Petitioners have failed to establish the fifth *Loving*/second *Althen* prong.

G. *Loving* Prong Six/*Althen* Prong Three

The final *Loving* prong requires Petitioners to establish a "proximate temporal relationship" between the significant aggravation of A.S.'s condition and the vaccines she received. *Loving* at 144; *see also Althen*, 418 F.3d at 1281. Petitioners must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *de Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008).

The timing prong contains two parts. First, Petitioners must establish the "timeframe for which it is medically acceptable to infer causation" and second, they must demonstrate that the onset of the disease occurred in this period. *Shapiro v. Sec'y of Health & Hum. Servs.,* 101 Fed. Cl. 532, 542-43 (2011), *recons. denied after remand on other grounds*, 105 Fed. Cl. 353 (2012), *aff'd without op.,* 503 F. App'x 952 (Fed. Cir. 2013).

Petitioners' theory of the case is premised on the fact that A.S. "fell off a cliff" neurologically. Dr. Kinsbourne's opinion on onset is consistent with this theory. He stated that the "onset of [A.S.'s] epileptic encephalopathy was abrupt, within hours of her vaccinations. Such brief intervals are typical for pertussis vaccine encephalopathies. Thus the onset of [A.S.'s] encephalopathy occurred within a medically reasonable temporal interval after the vaccinations." First Kinsbourne Rep. at 6. As discussed in this decision, I do not find that A.S. suffered from an abrupt neurological decline, and instead find that her deterioration began at around the age of four months and gradually progressed. Because I do not find that the onset of A.S.'s condition occurred during the "timeframe for which it is medically acceptable to infer causation," Petitioners have not presented preponderant evidence with respect to the sixth *Loving*/third *Althen* prong.

VII. CONCLUSION

Petitioners have experienced great suffering as a result of A.S.'s condition. However, in order to find they are entitled to compensation they must preponderantly demonstrate that the vaccines caused the significant aggravation of A.S.'s condition. Based on the evidence presented in this case, I conclude that Petitioners have not made such a showing. **Their petition is therefore DISMISSED. The clerk shall enter judgment accordingly.**[12]

IT IS SO ORDERED.

s/ Katherine E. Oler
Katherine E. Oler
Special Master

[12] Pursuant to Vaccine Rule 11(a), the parties may expedite entry of judgment by each filing (either jointly or separately) a notice renouncing their right to seek review.